UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

IMPACT OF MATERNAL WEIGHT ON BODY COMPOSITION AND WEIGHT OF THE INFANT

A DISSERTATION

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

degree of

Doctor of Philosophy

By

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Norman, Oklahoma
2007

IMPACT OF MATERNAL WEIGHT ON BODY COMPOSITION
AND WEIGHT OF THE INFANT

A DISSERTATION APPROVED FOR THE
DEPARTMENT OF HEALTH AND EXERCISE SCIENCES

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ACKNOWLEDGMENTS

First, I would like to thank Dr. David Fields for his continual support and advice through this very long journey. It has been bumpy at times; however, I am grateful for everything you have taught me and every opportunity you have given to me. I truly would not be where I am if it were not for you. A very special thank you also goes to Dr. Mary Dinger for providing guidance and advice when I desperately needed it. You were a kind listener that provided wise advisement. Further, I would like to thank the remainder of my committee members, Dr. Allen Knehans, Dr. Joel Cramer and Dr. David Thompson, for taking time out of their very busy schedules to serve as committee members for this project. Help and support was also found from Lauren Pratt by providing assistance with data collection and recruitment. Her support was invaluable and I greatly appreciate it. Inspiration and continual encouragement was always given from my parents, Leland and Dolores Hyde. They taught me at a young age that I could do and be anything that I desired and to never give up on my dreams. Thank you for instilling that drive into me. The greatest inspiration I have in life is from my best friend and loving husband. Casey has always supported me in my quest for education and in my career goals. I love you more than words can begin to express and this would have never been accomplished without your love and support.

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ABSTRACT

Objective: The purpose of this study was to compare body weight and composition (%fat, fat mass, and fat-free mass) in neonates born to mothers with a normal pre-gravid BMI (<25 kg/m^2) versus neonates born to mothers with an overweight/obese pre-gravid BMI (≥25 kg/m^2).

Study Design: Seventy-two neonates (33 from normal mothers and 39 from overweight/obese mothers) of singleton pregnancies with normal glucose tolerance had their body weight and body composition assessed by air-displacement plethysmography.

Results: After controlling for neonate age at time of testing, significant differences were found between groups for %fat (12.5 ± 4.2 % vs. 13.6 ± 4.3 %; $P \leq 0.0001$), fat mass (414.1 ± 264.2 g vs. 448.3 ± 262.2 g; $P \leq 0.05$) and fat-free mass (3310.5 ± 344.6 g vs. 3162.2 ± 343.4 g; $P \leq 0.05$), with no significant differences between birth length (50.7 ± 2.6 cm vs. 49.6 ± 2.6 cm; $P = 0.08$) or birth weight (3433.0 ± 396.3 g vs. 3368.0 ± 399.6 g; $P = 0.44$).

Conclusions: Neonates born to mothers who have a normal BMI have significantly less total and relative fat, and more fat-free mass than neonates born to overweight/obese mothers. Though preliminary, these data suggest that the antecedents of future disease risk (e.g. cardiovascular disease, diabetes, and obesity) occur early in life.

CHAPTER I

INTRODUCTION

Adult obesity has risen rapidly over the past thirty years with 1 in 3 adults classified as obese (1). Overweight and obesity have been linked to the development of disorders such as hypertension, dyslipidemia and insulin resistance, referred to collectively as the metabolic syndrome (2). The primary outcome of the metabolic syndrome is cardiovascular disease leading to impaired health and possible early mortality. The same staggering statistics and disorders are found in overweight children and adolescents as well. Currently, 30% of children are classified as at risk for overweight while 17% are overweight (1) and more startling is the greatest increase in overweight was seen in preschool children (3).

The complications of overweight in children are similar to those found for adults (4, 5). Overweight in children is related to dyslipidemia, elevated blood pressure and impaired glucose tolerance (6, 7). Unfortunately, the early onset of type 2 diabetes is associated with a more aggressive type of cardiovascular disease later in life (8). Obesity alone is attributed to an annual 300,000 deaths per year while type 2 diabetes is the 6^{th} leading cause of death (9, 10).

With the rapid increases in obesity rates, a first ever decline in life expectancy is predicted, especially among young obese adults (11, 12). Due to its detrimental health effects, the root cause of the rise in obesity and the related disorders in adults and overweight in children is vehemently being studied. Though the obesity crisis is clearly visible, the mechanisms underlying the development of obesity are poorly understood.

In an attempt to discern critical periods for obesity development, recent research has focused on the intrauterine environment and its importance on obesity development and the metabolic outcome of the infant (13). The Barker Hypothesis or "fetal origins hypothesis" (14) proposes that diseases manifesting in childhood and adulthood are actually "programmed" from restraint of growth during fetal life and infancy. "Programmed" refers to the induction, deletion or impairment of development of organ structure by an early insult or stimulus during gestation or critical periods of early life that cause permanent or long term changes in the structure or function of an organism (15, 16).

The intrauterine environment is assessed crudely by the birth weight of the infant. However there are issues when using birth weight as an indicator of nutrition status (17). For instance, low birth weight during gestation is defined as a birth weight below 2500 grams or a preset percentile such as 3^{rd}, 5^{th} or 10^{th} percentile (18). However, just using these parameters does not distinguish how these infants arrived at this birth weight. For example, there may have been an impact of poor maternal nutrition or simply these babies may have reached their genetic growth potential (17). At this time, a routine clinical measure does not exist to distinguish these factors.

The perinatal mortality rate is six to ten times higher in low birth weight infants than those infants born at a normal birth weight (17). Small birth size and disproportion in length, head size and weight indicate an inadequate supply of nutrients and oxygen during stages of gestation (14). These abnormalities in growth reflect the adaptations the fetus made to survive during development. However the conditions the fetus is exposed to during development, under or over-nutrition may not be permanent. Instead, many

times the environment is one of nutrition abundance. On the converse, over-nutrition during gestation results in fetal overgrowth termed macrosomia which is defined by a birth weight greater than 4000 grams or large for gestational age where weight exceeds the 90th percentile based on population norms. A high birth weight due to over-nutrition during gestation increases the chance of obesity development, type 2 diabetes and the metabolic syndrome later in life (13).

Low birth weight is associated with the development of respiratory distress syndrome, hypoglycemia, hypocalcemia, hyponatremia and coronary heart disease (14, 18). Additionally, studies have identified a high birth weight relating to an increased risk of overweight in adolescence (19-21). Other studies have identified a low birth weight relating to development of type 2 diabetes, increased risk of obesity development and the metabolic syndrome (19, 22-25).

Furthermore, research has shown a direct relationship between maternal obesity and the development of obesity and metabolic disorders in offspring (26-30). However, scarcity in food in developed nations is not currently a problem, rather there are conditions of an abundance of food. In infants exposed to an adverse intrauterine environment leading to a low birth weight, an over abundance of food presents a problem. Their bodies were programmed to survive and to efficiently use all nutrients. Therefore, their bodies lack the ability to handle an abundance of nutrients therefore increasing the risk of coronary heart disease, diabetes and obesity stemming from the adaptations to survive developed during gestation (15).

Even though epidemiological studies have suggested a relationship between birth weight and development of disease in adulthood, some research finds no relationship to birth weight and future disease development in the offspring (31-35). Studies examining subjects exposed to malnutrition during pregnancy due to famine during the sieges of Leningrad (35) and Finland (33) found no effect of the famine on disease development in adulthood. Other research (32) suggests inadequate nutrition during pregnancy may affect later health in adulthood indirectly and not directly by affecting birth weight of the offspring. Therefore, solely using birth weight as an indicator of the relationship may underestimate the true association.

The prevalence of obesity in American women aged 20-39 during reproductive years is 30% (1), so many females enter into pregnancy in an obese state putting themselves at risk for metabolic complications and poor pregnancy outcomes (36, 37). In the United States, the rate of low birth weight is fairly low, occurring only during 5% of all pregnancies (38). In fact, over the last 25 years, the mean weight of females at their first prenatal visit has increased 20% as well as the percent of women with a BMI greater than 29 kg/m^2 (39). Studies in both North America and Europe have reported an increase in mean birth weight, with those greater than the 90^{th} percentile for gestational age or classified as macrosomic increasing the most (40, 41).

Furthermore, recent work has shed light on possible physiological outcomes of the infant due to maternal over-nutrition. In an Italian population, maternal hypercholesterolemia was related to increased rates of fatty streaks of the fetus in a post mortem study (42, 43). Studies of Pima Indians shows a high likelihood of maternal diabetes being passed to the offspring (44). Research has yet to elucidate the exact

physiological mechanisms underlying changes in the offspring due to maternal over nutrition during pregnancy.

Maternal overnutrition is suggested to affect the development of several systems and organs in the offspring. They include the appetite regulating network (45-50), the cardiovascular system (42, 51, 52) and the pancreas affecting insulin sensitivity (51, 53, 54). In rodent models that explored effects of development of appetite control, research shows specific areas of the brain to be affected (55, 56). Therefore, in cases of over-nutrition, the satiety signals are not recognized (46, 55, 56). Maternal over-nutrition (53, 54) is also related to fetal insulin resistance, greater circulating levels of leptin and higher levels of resting glucose and insulin in offspring. Impairment of pancreatic beta cells and structural changes in the pancreas has been found. Regulation of blood pressure is also affected by in utero exposure to maternal over nutrition (52, 57) through an inability of baroreceptors to function and control blood pressure (57). Additionally, vasodilation in offspring is blunted, the fatty acid content of the aorta was abnormal and elevated levels of triglycerides and reduced levels of HDL were detected in offspring of overnourished mothers (52).

The divergent views regarding the relationship between an adverse intrauterine environment and the development of obesity and related disorders in the infant emphasizes the need to further understand how maternal BMI impacts outcomes in the offspring. Research suggests a relationship between maternal obesity and large for gestational age and later development of obesity in the offspring (30, 58). However, only one study has quantified infant body composition related to maternal BMI (59). The purpose of this study was to compare infant body composition and body weight of

mothers categorized as normal and overweight/obese based on pre-gravid body mass index (BMI).

Purposes

1. The purpose of this study was to compare birth weight in neonates from mothers who are classified as having either a normal (<25 kg/m^2) or overweight/obese (≥25 kg/m^2) pre-gravid BMI.
2. A second purpose was to compare body composition in neonates from mothers who are classified as having either a normal (<25 kg/m^2) or overweight/obese (≥25 kg/m^2) pre-gravid BMI.

Research Questions

1. Does neonatal birth weight differ between mothers who have a normal (<25 kg/m^2) or overweight/obese (≥25 kg/m^2) pre-gravid BMI?
2. Does neonatal percent body fat differ between mothers who have a normal (<25 kg/m^2) or overweight/obese (≥25 kg/m^2) pre-gravid BMI?
3. Does neonatal total fat mass differ between mothers who have a normal (<25 kg/m^2) or overweight/obese (≥25 kg/m^2) pre-gravid BMI?
4. Does neonatal fat-free mass differ between mothers who have a normal (<25 kg/m^2) or overweight/obese (≥25 kg/m^2) pre-gravid BMI?

Hypotheses

1. Neonates from overweight/obese mothers will weigh significantly more than neonates born to normal pre-gravid BMI mothers.
2. Neonates from overweight/obese mothers will have a significantly higher percent body fat than neonates born to normal pre-gravid BMI mothers.

3. Neonates from overweight/obese mothers will have significantly higher fat mass than neonates born to normal pre-gravid BMI mothers.
4. Neonates from overweight/obese mothers will have significantly lower fat-free mass than neonates born to normal pre-gravid BMI mothers.

Significance of the Study

While birth weight provides a crude, simple and indirect assessment of intrauterine environment, body composition assessment provides a more detailed understanding of the relationship between birth weight and obesity programming in early life.

Delimitations

1. Healthy male and female full-term infants with a gestational age of ≥37 weeks and ≤42 weeks.
2. Infants whom were ≤35 days old.
3. Mother at the time of delivery is between the ages of 18-45 years old.
4. Infants with a prolonged medical stay defined as >4 days.
5. Tobacco use by the mother during pregnancy.
6. Excessive alcohol consumption during pregnancy defined as >1 drink a week.
7. Infants with presumed or known chromosomal or severe congenital abnormalities will not be allowed to participate.
8. Infants from mothers with type 1, type 2 or gestational diabetes.

Limitations

1. The subject sample was limited to the surrounding communities of Oklahoma City, Oklahoma.

2. Many in the subject sample may be affiliated with University of Oklahoma Health Sciences Center clinics and uninsured.

Assumptions

1. All mothers reported medical history concerning birth (length of gestation, pre-gravid body weight and height, pregnancy weight gain) honestly and accurately.
2. Infants are healthy and free of disorders that could affect intrauterine growth and metabolism.

Operational Definitions

1. Pre-gravid – Prior to pregnancy.
2. Gestation – During pregnancy.
3. Prenatal – Occurring, existing, or performed before birth.
4. Pea Pod® - Trademark name for the only commercially available system to assess infant body composition using air displacement plethysmography made by Life Measurement Incorporated, Concord, CA.
5. Plethysmography – A technique referring to the measurement of size or volume by using the pressure volume relationship (60).
6. Macrosomia – A birth weight greater than 4000 g (18).
7. Large for gestational age – A birth weight that exceeds the 90^{th} percentile for population based norms (18).
8. At risk for obesity – A length for height greater than or equal to the 95^{th} percentile.

CHAPTER II

REVIEW OF LITERATURE

The intention of this study was to examine the effects of an adverse intrauterine environment on development of obesity in infants. The primary purpose of this study was to compare infant body weight and composition from mothers who have a normal or overweight/obese pre-gravid BMI.

Assessment of Infant Body Composition

Assessing body composition in infants using sophisticated methods presents technological, ethical and practical limitations therefore few research studies have thoroughly explored this topic. Though with the concurrent epidemic in childhood obesity and type 2 diabetes, the knowledge gained through assessment of infant body composition could be beneficial to determine if early life events influence or are related to the development of these disorders. Though birth weight does provide a crude estimate of conditions experienced by the infant in utero, quantification of fat and fat-free mass may provide a description of any underlying relationships.

All body composition methods assess body fat indirectly and therefore are based on theoretical models (61). Special populations such as infants could potentially violate the underlying assumptions of the multi-component models. Thus the accuracy of the technique to assess body composition depends on the model and the associated assumptions. When assessing body composition in infants, special consideration must be taken into account when selecting a technique. Various methods have been used to assess body composition in infants such as anthropometry (62-66), magnetic resonance imaging (MRI) (67), total body water (TBW) (67-70), total body potassium (TBK) (68,

70), total body electrical conductivity (TOBEC) (64, 68, 69, 71, 72), dual energy x-ray absorptiometry (DXA) (62, 65, 66, 68, 73, 74) and densitometry using air displacement plethysmography (75-78). Research has suggested that densitometry is a method that holds promise for a safe, quick and easy assessment of infant body composition (75). The only method based on densitometry and used for infant body composition assessment is the Pea Pod® using air displacement (75). The following paragraphs will summarize research studies using the various methods described previously to assess infant body composition.

A very simple method to assess changes in body mass is measuring length, body weight or skeletal width (61). Changes in anthropometrics are assumed to represent changes in fat mass and fat-free mass however circumference or skinfold thickness are needed to better distinguish changes in fat and fat-free mass (79). Numerous studies have validated various anthropometrics to either total body water (80, 81), total body electric conductivity (64, 72, 80, 81) or dual energy x-ray absorptiometry (62, 65, 66).

Davies and Lucas (81) validated the Quetelet's index with total body water in male and female infants at 5 and 11 weeks. They found Quetelet's index to be a poor predictor of body fatness. In a second study by the same group (80), they compared skinfold thickness to total body water in infants at 5, 11 and 26 weeks and again found skinfold thickness to be an inaccurate method to predict fat mass. Total body water (TBW) has also been used to validate the use of skinfold thickness to estimate fat mass (63). Poor agreement was found with TBW and skinfold thickness overestimated body fat at low ranges of body fat and underestimated body fat at higher values of body fat.

Other research compared anthropometric predictive equations by Westrate et al. (82) and Dauncey et al. (83) to TOBEC in 435 infants (64). Both equations showed poor agreement with fat mass results from TOBEC. However, research by de Bruin et al. (72) compared upper-arm anthropometry, Quetelet's index, weight by length and skinfold circumferences at five sites (biceps, triceps, subscapular, suprailiac and quadriceps) to TOBEC in 435 infants. TOBEC fat mass measurements correlated strongest with weight for length and calf circumferences however, researchers recommended using any of the anthropometric methods as only rough estimates of fat mass in infants.

Dual energy x-ray absorptiometry (DXA) has been used to assess the ability of anthropometric measures to assess fat mass in infants (62, 65, 66). In contrast to other studies validating anthropometrics, these studies all found agreement between their measurements and DXA. Koo et al. (66) assessed 214 infants and found weight and length best agreed with DXA for prediction of fat mass (adjusted R^2>0.85). Similarly, two studies comparing weight, length and skinfold thickness at the triceps, biceps, suprailiac and subscapular and found skinfold thickness best agreed with DXA (62, 65). Butte et al. (68) compared TBW, TBK, TOBEC and DXA in 76 healthy term infants at various time points during the first two years of life. Significant differences were found between all methods and wide limits of agreement suggest these methods cannot be used interchangeably and researchers concluded further development and validation of body composition methods in infants is needed.

Air-displacement holds promise as a simple, quick and reliable method to assess body composition in infants (75). Sold commercially as the Pea Pod®, measurement of body composition involves assessment of body mass and body volume. Completion of

the entire testing procedure can be done in five minutes. Since being introduced in 2003, few studies have been done using air displacement in infants (76-78). Sainz and Urlando (76) used 24 phantoms made from pig muscle and fat to assess the precision and accuracy of the Pea Pod® compared to chemical analysis and hydrostatic weighing. No differences were found between the Pea Pod® and chemical analysis with mean percent fat values of 18.55% and 18.59%, respectively. Percent fat measurements from all three methods were highly correlated ($r>0.90$; $P<0.0001$). Using regression analysis with chemical analysis as the reference method, no difference was found from the line of identity indicating agreement between percent measures by the Pea Pod® and chemical analysis. Bias was assessed between Pea Pod® and chemical analysis with results indicating high agreement and no systematic bias in differences across a wide range of mass and percent fat ranges (76).

Yao et al. (78) assessed within and between day reliability in 17 infants on two consecutive days. Results indicated the mean differences in percent fat for day one (-0.39±0.81) and day two one (-0.27±0.97) were not different from zero and the percent fat 95% limits of agreement for within and between day tests were narrow (-2.0-1.2 and -2.2-1.7, respectively). Between and within day reliability as well as accuracy was also assessed by a second study (77). No differences were found for percent fat between days or within days (-0.5±1.21 %fat and 0.16±1.44 %fat, respectively). In addition to assessing validity and reliability, accuracy of body fat measures from the Pea Pod® were compared to body fat measures from TBW using deuterium (^2H_2O). No difference was found between mean percent body fat from air displacement and TBW (20.32 %fat vs. 20.39 %fat). The 95% limits of agreement were calculated between the two methods (-

6.84 %fat, 6.71 %fat) and were lower than reported for other methods to assess body composition in infants. Regression analysis found high agreement (R^2=0.76) between methods and a low SEE (3.26) (77). Thus, the authors concluded air displacement is an accurate and reliable method to assess body composition in infants.

Metabolic and Hormonal Occurrences and Disturbances during Pregnancy

During pregnancy, several complex hormonal and metabolic adaptations occur to ensure proper growth and survival of the developing fetus (84). Human chorionic gonadotropin, progesterone, estrogens, human chorionic somatomammotropin, prolactin, relaxin and inhibins are a short list of hormones that increase and work to maintain the pregnancy and ensure optimal growth. There are specific endocrine functions that change during a normal pregnancy and possibly most significant are changes in the function of the pancreas; specifically the beta cells (84). Maternal insulin sensitivity is normal or even enhanced during the first trimester however, during the second and third trimesters insulin sensitivity is greatly decreased (85). Catalano et al. estimated reductions of insulin sensitivity by 47% in obese women and a 56% reduction in insulin sensitivity in normal weight women (86, 87). Therefore in response to increased insulin sensitivity, human chorionic somatomammotropin direct the beta cells to increase production of insulin to compensate for this decline in insulin sensitivity. Furthermore, estrogen, growth hormone, corticotropin-relasing hormone and progesterone allow energy production utilization to shift from primarily carbohydrates to lipids thus making glucose readily available to the fetus (85). Pregnancy is therefore characterized by increases in blood glucose levels and modifications of circulating cholesterol, triglycerides, free fatty acids and phospholipids. Several glucocorticoids are also

elevated during this time and are thought to contribute to maternal adipose tissue gain and mammary gland development (84). These metabolic adaptations are necessary to support the increased energy demands during pregnancy as well as prepare the maternal system for delivery and lactation (85).

When metabolic and hormonal adjustments fail to overcome insulin resistance due to pregnancy and the beta cells cannot maintain maternal glucose within normal values, gestational diabetes develops (88). Gestational diabetes is simply defined as any degree of glucose intolerance first recognized during pregnancy (89). This type of glucose intolerance affects approximately 7% of all pregnancies and can carry short and long term complications (88). Those with gestational diabetes are at increased risk for pregnancy induced hypertension, toxemia and delivery by caesarean section (88) as well as subsequent development of type 2 diabetes (85).The infant of a gestational diabetic is at increased risk for macrosomia, neonatal hypoglycemia, hyperbilirubinemia, hypocalcemia and polycythemia (88).

Compounding the situation and effects of gestational diabetes is maternal obesity (90). Though there are many associated risks during pregnancy with gestational diabetes, maternal obesity can carry similar and independent risks. The prevalence of obesity in women of reproductive age is 30% (1) therefore pre-gravid overweight is one of the most common high risk obstetric complications (37). Many associate obesity as being related to development of disorders later in life, however a small increase in weight prior to pregnancy relates to increased risk for development of gestational diabetes and hypertension during pregnancy (37).

There are several obstetric complications that can develop during pregnancy due to maternal obesity that can affect the health of the mother as well as the health of the infant (90). Generally, complications during pregnancy are due to an excessive pre-gravid BMI rather than excessive weight gain during pregnancy (90). There are recommendations for healthy weight gain during pregnancy based on weight of the mother before pregnancy. The Institute of Medicine recommends for women who enter into pregnancy at a normal weight to gain 25-35 lbs, women who are overweight to gain 15-25 lbs and women who are obese to gain 15 lbs (91). Possibly more discerning than weight gain, is fat mass changes during pregnancy. Ehrenberg et al. (92) examined women by pre-gravid weight status to determine which grouped gained the greatest percent body fat. Results found lean subjects gained greater percent fat compared to obese subjects however similar amounts of fat mass and fat-free mass were gained (92).

Specific complications during pregnancy that can occur in overweight and obese women include increase risk of miscarriage, gestational hypertension, pre-eclampsia and gestational diabetes (90). Mothers who are obese prior to pregnancy or develop gestational diabetes during pregnancy tend to have larger babies and therefore are at increased risk for caesarean delivery and the associated morbidities of this type of delivery (90). Aside from the risks presented to the mother's health, there are fetal risks associated with maternal obesity as well. Obese mothers are more likely to bear a child with low Apgar scores, neural tube defects and macrosomia (37). The detection of fetal abnormalities during gestation is difficult in women with increased central adiposity possibly delaying necessary medical care. Due to women with a greater pre-gravid BMI

giving birth to larger babies, there are long term health risks such as increased risk of obesity, hypertension and diabetes for the infant in adulthood (19, 22).

Studies in both North America and Europe have reported an increase in mean birth weight, with those greater than the 90th percentile for gestational age or classified as macrosomic increasing the most (40, 41). Insulin resistance is normal during pregnancy, however, in obese pregnancy women insulin resistance is increased even greater (86, 87). Therefore, the fetus is exposed to all major fuel sources, glucose, free fatty acids, ketones and amino acids. This is a major contributing factor to obese pregnant women delivering infants that are large for gestational age (37). Furthermore, increases in the flow and availability of substrates from the mother decreases release of placental growth suppressive peptides. These peptides are responsible for enhancing fetal growth rate through increasing expression of insulin like growth factors and decreasing their binding proteins (93). Therefore, the increasing prevalence of macrosomia in obese women is due to a shift and increase in fuel metabolism. In models to predict macrosomia, the addition of hyperlipidemia further verifies large birth weights therefore increased lipids, as well as increased glucose, contribute to large infants (93).

Fetal Programming of Obesity Development

Critical periods for obesity development have been identified; gestation, early infancy, the period of adiposity rebound around 5 years and adolescence (13). As will be discussed below with the fetal origins hypothesis, prenatal or perinatal undernutrition can adversely impact the health outcome of the infant during adulthood (13). Studies of pregnant women from times of war or famine provide insight into the effect of abnormal nutrition on the health outcome of the infant (94). The prevalence of obesity was greatest

in offspring conceived during the Dutch famine than those who were conceived before of after.

Birth weight of the infant is used as a crude measure of the intrauterine environment and research has shown a low or high birth weight is related to an increase in the chance of obesity development, type 2 diabetes and the metabolic syndrome later in life (19, 22-25). Maternal obesity is also related to the development of obesity and metabolic disorders in the offspring (26-30). In addition, an altered maternal-fetal glucose metabolism has been shown to influence infant birth weight and obesity development as seen during gestational diabetes (20). Offspring exposed to an intrauterine environment of gestational diabetes have an increased risk of developing later obesity and type 2 diabetes (26, 28).

Though epidemiological studies have suggested a relationship between birth weight and development of disease in adulthood, some research opposes these hypotheses (31-35). Stanner et al. (35) studied 169 subjects exposed to famine during the siege of Leningrad in 1941 to 1942. They compared three groups: subjects exposed to famine in utero, subjects exposed to famine as infants and a subjects born at the same time but outside of the area under siege. No differences were found between those exposed to starvation in utero or during infancy for glucose tolerance, insulin concentration or blood pressure. A relationship between blood pressure and adult obesity was found in the first group suggesting famine exposure in utero and adult obesity acted synergistically to increase hypertension development.

A similar study was performed to examine those exposed to famine in Finland from 1866 to 1868 (33). Finnish vital statistics were used to compare those born before

and after the famine to those born during the famine. Mortality was compared at age 17 years, 17 to 40 years, 60 years and 80 years. No difference in mortality was found between the three groups at subsequent ages, including old age. A recent article by Painter et al. (95) reports results from 975 subjects who survived the Dutch famine between 1944 to 1945 and risk of coronary artery disease (CAD) development in adulthood. Of the 975 subjects, only 83 subjects were diagnosed with CAD and overall analysis showed a weak relationship between birth weight and CAD development. However a subgroup analysis breaking subjects into five groups based on time of exposure to famine found a difference based exposure rate for CAD development compared to no famine exposure. Authors conclude a significant affect of malnutrition and later CAD development in adulthood, though the small numbers within groups may confound their conclusions.

Other researchers (32) suggest inadequate nutrition during pregnancy may affect later health in adulthood indirectly and not directly by affecting birth weight of the offspring. Therefore, solely using birth weight as an indicator of the relationship may underestimate the true association. Furthermore, early research by Moulton used autopsy of stillborn babies categorized by small-, appropriate- or large for gestational age to quantify accretion of fetal fat (96). The lean body mass was relatively consistent between all three groups; however the large for gestational age group had the greatest amount of fat accretion. The divergent views regarding the relationship between an adverse intrauterine environment on development of obesity and related disorders in the infant emphasizes the need to further understand how maternal BMI impacts health of

the offspring. At this time, only one study has quantified infant body composition and used this information to discern a relationship with maternal BMI (59).

Disease Development Related to Low Birth Weight

With the prevalence of obesity and related disorders continually increasing over the last thirty years in both adults and children, urgency has been placed to find cause for these rapid changes with far reaching implications (1). Based on large cohort epidemiological studies, the idea that the intrauterine environment impacts the development of adult disease was developed (97-103). Within epidemiological studies, a theme emerged; links were made between adult disorders and body size at birth. With this idea, hypotheses were proposed by Hales and Barker termed the fetal or developmental origins hypothesis (15). These hypotheses suggest that adult disease is a result of growth restraint during gestation due to malnutrition of the mother or impaired nutrient transfer to the fetus. Undernutrition is thought to cause an insult during a critical period of early life to the fetus that leads to a "programmed" effect. "Programmed" refers to the induction, deletion or impairment of development of organ structure by an early insult or stimulus during gestation or critical periods of early life that are permanent or cause long term changes in the structure or function of an organism (15, 16).

Fetus exposure to an intrauterine environment of undernutrition will result in physiological adaptation to ensure survival (15). During adaptation, the fetus optimizes the restricted nutrient supply by favoring the development of some organs over others therefore preserving the development of critical organs such as the brain over the development of less critical organs such as the pancreas, liver, kidneys and muscle. This

altered growth leads to changes in the metabolism, perfusion and innervation of developing tissues (15). Critical periods for tissue growth and rapid cell division have been identified where organs differentiate and mature for survival after birth. Exposure to undernutrition during this time may have long lasting consequences on organ function making the fetus susceptible to development of disease later in life during adulthood (15).

Examples of organs hypothesized to be affected by undernutrition are the pancreas and liver, both important for metabolic balance and the kidneys and circulatory system, both important for blood pressure maintenance (15, 104). Specifically, the beta cells of the pancreas are sensitive and damage to the vasculature and innervation of the beta cells due to suboptimal nutrition, give rise to defects of structure and function of the pancreas (15). This impairment results in insufficient insulin release causing hyperglycemia and eventual beta cell burnout in efforts to control high blood glucose concentrations (105). Therefore, impairment of the function of the pancreas results in a predisposition for development of type 2 diabetes. This damage is exacerbated by age and a natural decline in organ function. Furthermore, the body has programmed itself to survive in an environment of little nutrition (15). However, lack of food is not currently a problem in most developed nations; instead there is an abundance of food and a lack of physical activity.

Fetal malnutrition is also related to a diminished development and function of other organs such as the liver, kidneys and circulatory system involved in the control of blood pressure (104). Infants who were malnourished in utero have a decline in the number of nephrons (106) and elastin in the vessel walls leading to impairment of the

regulation of blood pressure (107). With a decline in the number of nephrons, an increase in glomerular filtration rate in the remaining nephrons is increased due to the diminished number (17). This results in an increased nephron flow and glomerular volume resulting in focal glomerulosclerosis or nephron loss. The ultimate end result is an inability to regulate increases in blood pressure and therefore hypertension develops (17). Further evidence is found in ultrasound studies that have examined growth rates of the fetal kidneys between small and appropriate for gestation age infants (108). Results indicate the growth rate of the kidneys was slower in small for gestational age infants and differences between groups were greatest between 26 and 34 weeks gestation. Furthermore, differences in kidney size after birth was detected with smaller size detected in small for gestational age infants compared to appropriate for gestational age infants (108).

Other research regarding development of hypertension in adulthood found impairment of endothelial dependent vasodilation mediated by nitric oxide in low birth weight infants (109, 110). Research indicates that the sympathoadrenal system is also affected in low birth weight infants (111). In a cohort of 449 male and female adults, ranging in age from 46 to 54 years, resting pulse rate, blood pressure and birth weight were recorded. Resting pulse decreased 76 beast per minute in those who weighed 2.5 kg or less at birth and was correlated positively to systolic and diastolic blood pressure providing a possible relationship between low birth weight, elevated sympathetic nervous system activity and hypertension in adulthood (111). Galland et al. (112) found similar results when examining heart rate variability between small and appropriate for

gestational age infants. Though they found the autonomic component was lower in small for gestational infants, the sympathetic component of heart rate variability was higher.

Other physiological mechanisms hypothesized to be caused due to an adverse intrauterine environment include a failure to develop proper appetite regulation (94). Therefore, undernutrition in utero results in a failure of the hypothalamic centers to develop thus resulting in an inadequate control of food intake. Undernutrition during the third trimester may result in decreased adipocyte differentiation and undernutrition during the first or second trimester may result in increased adipocyte differentiation. Therefore, undernutrition early in gestation would result in impaired regulation of food intake and predispose to obesity in adolescence or adulthood.

Skeletal muscle is important for glucose disposal given that the majority of post prandial glucose is taken up by the skeletal muscle (17). In utero determination of primary muscle fibers is formed in humans during two phases starting between weeks 6 and 8 in gestation and completing by week 18. Research suggests that genetics determines the number of primary fibers however; secondary fiber amount is affected by environment (17). Maternal malnutrition has been shown to affect number of fetal fibers (113, 114). Research indicates that reduced nutrient supply to the fetus can alter muscle fiber number by reducing the total count. Therefore, given that muscle functions as a large site for glucose uptake, reduced fibers could easily contribute to hyperglycemia and insulin resistance.

Another important organ involved with metabolic control and hypothesized to be affected by intrauterine growth restriction is the liver (17). In rat models, research (115) has shown growth retarded rats have a decreased oxidative phosphorlyation and

therefore less ATP generation, and this is further exacerbated by the fact that redox states are uncoupled in the liver and therefore less ATP is generated per molecule of glucose. Further research in rat models have found an upregulation in hepatic gluconeogenic enzymes (116) therefore increasing glucose release from the liver and contributing to insulin resistance. Maternal malnutrition has also been suggested to program the offspring for increased hepatic fatty acid synthesis thus increasing hepatic triglycerides (117). Increased hepatic triglycerides are thought to contribute to decreased skeletal muscle insulin sensitivity therefore sparing glucose to use in support of growth in utero for vital organs such as the brain.

The human hypothalamo-pituitary-adrenal (HPA) axis begins to develop early in fetal life and further develops in the postnatal period (118, 119). Activation of the HPA axis results in release of glucocorticoids, which is mainly cortisol in humans (120). This is important because increased HPA activation and therefore cortisol release in humans in related to increased risk of development of atherosclerosis, hypercholesteremia and type 2 diabetes. Epidemiological research has indicated relationships between birth weight, plasma cortisol and the development of hypertension and type 2 diabetes (121, 122). There are several maternal prenatal stressors that can affect the programming of the HPA axis in the offspring including maternal stress, increased exposure to glucocorticoids in utero and maternal malnutrition (119). It is not entirely understood how prenatal stress affects development of the HPA axis in the offspring, though it is thought stress causes changes in maternal cardiovascular and endocrine features. Stress during pregnancy can increase the release of ACTH, beta-endorphin, glucocorticoids and catecholamines though the placenta forms a structural and biochemical barrier to many

of these factors (119). Even so, several will still cross and reach the developing fetus. Furthermore, catecholamines can result in constriction of blood vessels therefore causing fetal hypoxia which will stimulate the fetal HPA axis (119).

Even though several factors are thought to adversely affect HPA axis due to prenatal stress, glucocorticoids are the primary candidate (119). During pregnancy, glucocorticoids function to maintain normal development of the brain however consistent sustained high levels of glucocorticoid exposure to the fetus can modify brain structure and function (120). Furthermore, elevated glucocorticoid exposure during gestation is thought to compromise development of the hippocampus causing a cascade of events resulting in hippocampal deficit and extended HPA responses to stress and elevated cortisol exposure (119).

Another target for fetal programming of adult disease is the adipocyte and hormones secreted by the adipocyte. Leptin is a hormone secreted by the adipose tissue and acts to signal as to the amount of energy stores, specifically fat mass (17). Leptin binds at sites both centrally and peripherally to decrease food consumptions and increase energy utilization. Similar to having high circulating concentration of insulin in adult obesity, high amounts of leptin are also present during adult obesity and it is thought leptin resistance plays a role in obesity development (17). Hypotheses suggest high circulating levels of leptin cause an uncouple of the action of leptin at the hypothalamus therefore disturbing the signals that decrease appetite (123). There are leptin receptors located on the pancreatic beta cells and leptin will inhibit insulin secretion and stimulate adipogenesis of adipose tissue (124).

Due to the function of leptin, it is hypothesized that leptin plays a role in early programming of human obesity (17). A positive relationship exists between cord leptin at delivery and birth weight and body fat of the infant. In pregnancies complicated by altered metabolic control, the infant is born hyperinsulinemic and hyperglycemic and cord levels of leptin are positively related to infant body fat (125). Research shows low birth weight is associated to high levels of plasma leptin, even when controlling for degree of adult obesity (126).

Disease Development Related to High Birth Weight

Many studies have established a link between low birth weight and adult disease development (35, 97, 98, 103), however only 5% of infants in the United States are born with a low birth weight (38). We are instead faced with conditions of over abundance of nutrition and an obesity crisis. The prevalence of obesity in women aged 20-39 during reproductive age is 30% (1) therefore many females enter into pregnancy in an obese state putting themselves at risk for metabolic complications and poor pregnancy outcomes (36, 37) . Furthermore, recent research has shown over the last 25 years, the mean weight of females at their first prenatal visit has increased 20% as well as the percent of women with a BMI greater than 29 kg/m^2 (39). These increases were related to increased risk for these women of gestational diabetes and delivering a large for gestational age infant.

Just as undernutrition can have a detrimental impact on later health, research suggest overnutrition during prenatal and perinatal periods can have similar detrimental health effects on the infant (45-50, 127, 128). Overnutrition before and during pregnancy is associated with delivering large for gestational babies (>4000 grams). A high birth

weight due to over-nutrition during gestation is shown to increase the chance of obesity development, type 2 diabetes and the metabolic syndrome later in life (13). Overnutrition late in gestation may change adipose tissue differentiation and promote obesity in adolescence or adulthood (94).

Though many studies have examined the relationship between under nutrition and adult disease, few studies have examined over nutrition and the impact of fetal health in adulthood. Research has shown maternal health is related to health outcomes in the infant. In an Italian population, it was shown that hypercholesterolemia was related to increased rates of fatty streaks of the fetus in a post mortem study (42, 43). Evidence from population studies of Pima Indies shows a high likelihood of maternal diabetes being passed to the offspring (44).

The exact physiological mechanisms underlying changes to over nutrition during pregnancy are not as straightforward as under nutrition. Much of the information that has been gathered has been done in animal models of either rat, sheep or pig. There are several systems that are suggested to be affected by maternal over nutrition leading to offspring development of adult disease: appetite regulating network (45-50), cardiovascular system (42, 51, 52) and insulin sensitivity (51, 53, 54). Each one will be reviewed in the paragraphs below.

In rodent models exploring effects of development of appetite control, research shows specific areas of the brain to be affected (55, 56). The hypothalamic neural network integrates signals regarding energy status to send feedback to regulate food intake and energy expenditure (47). Appetite regulating neuropeptides are located in the arcuate nucleus of the hypothalamus and have projection extending to other hypothamic

nuclei that control the release of appetite suppressing and stimulating regulators. Appetite stimulators include neuropeptide Y and agouti-related peptide while the appetite suppressors are pro-opiomelanocortin derived neuropeptide alpha melanocortin stimulating hormone and cocaine and amphetamine regulated transcript (47).

Increased exposure of nutrition caused by over nutrition of the mother causes changes in the morphology of the areas of the brain responsible for control of appetite (46, 55, 56). Research has shown increases in the area of neuronal nuclei and cytoplasm within the paraventricular nucleus and ventromedical nucleus and decreases in the area of neuronal cytoplasm in the arcuate nucleus (56). These changes occur in concert with decreased sensitivity to leptin and insulin as well as to central hypothalamic neuropeptides. Therefore, in cases of over nutrition, the satiety signals are not recognized (46, 55, 56).

The pancreas and muscle are other organ systems suggested to be affected by maternal over nutrition (53, 54). Taylor et al. examined the impact of a maternal high fat diet derived from saturated fat on the metabolic outcomes of the offspring in a rat model (53). They found offspring of high fat mothers were more insulin resistant, had greater circulating levels of leptin and higher levels of resting glucose and insulin than controls. This group also showed impaired pancreatic beta cell insulin secretion and structural changes in the pancreas. Furthermore, the high fat offspring had higher levels of triglycerides and reduced levels of HDL cholesterol.

The cardiovascular system which regulates blood pressure is also suggested to be affected by in utero exposure to maternal over nutrition (52, 57). Research has shown an inability of female offspring of over fed mothers to regulate blood pressure due to

altered baroreceptor sensitivity (57). Ghosh et al. (52) studied vascular function of offspring from mothers that were fed a high saturated fat containing diet. Endothelial dependent vasodilation was blunted and there was a reduction in endothelial derived hyperpolarizing factor, involved with relaxation of the arteries, in offspring of the high saturated fat fed mothers. Furthermore, the fatty acid of the aorta was abnormal and elevated levels of triglycerides and reduced levels of HDL were detected (52).

There are many similarities of affects between offspring exposed to under nutrition and over nutrition. In regards to over nutrition, growing evidence is suggesting that saturated fat is most detrimental to development of offspring. More research is needed to clarify relationships.

Birth Weight Related to Later Body Mass Index in Adults

Birth weight is frequently used as an indicator of conditions experienced by the infant during gestation. The prenatal period has been indicated as a critical time for programming of later obesity development as suggested by the critical period hypothesis (13). This hypothesis proposes the intrauterine conditions the infant is exposed to may encourage obesity development throughout life. Thus, a higher birth weight is indicative of a positive intrauterine environment due to overnutrition whereas a low birth weight indicates a negative intrauterine environment due to undernutrition (129). Exposure to either a positive or negative intrauterine environment can adversely impact the health of the infant.

Several research studies have been performed to examine the relationship between birth weight and subsequent BMI in adulthood (19, 21, 22, 130-139). Many of these are large scale cohort studies using census or registry data to compare birth weight

to weight in adulthood. In one such study, Rasmussen and Johansson (21) used the Swedish Medical Birth Registry to identify 165,109 singleton male births between 1973 to 1976 and obtained height and weight data at 18 years from the Military Service Conscription Registry for the years 1990 to 1996. A direct relationship was found between birth weight for gestational age and BMI at age 18 years. Using multivariate analysis, a high birth weight was found to be a risk factor for risk of overweight (BMI > 25 kg/m^2) after controlling for living area, mother's age, educational level and number of births. Using birth weight between the 25^{th} and 50^{th} percentile as the reference category, those with a birth weight between the 95^{th} and 99^{th} percentile had an odds ratio for overweight of 1.50 while birth weight above the 99^{th} percentile had an odds ratio for overweight of 1.67. Similar odds ratios were found for severe overweight (21).

Sorensen et al. (137) linked the Danish medical birth registry to information obtained by the Danish draft board to obtain birth weight, height and weight data on 4300 males. The prevalence of obesity was calculated based on weight and length at birth. Results found a continual increase in BMI with increasing birth weight with 3.5% obese at birth weight ≤2500 grams to 11.4% obese at birth weight ≥4501 grams. Using multivariate analysis and controlling for mother's age, marital status and occupation, birth weight was found to be related to adult BMI (137). Analogous methods were used to study the impact of birth weight in Norway on subsequent BMI in adulthood in 348,706 males only (139). The Medical Birth Registry of Norway was used to collect birth weight while follow up height and weight were collected through registration with the military draft. A positive association was found between birth weight and adult BMI for birth weights >2500 grams.

Using similar methods to collect data, Tuvemo et al. (130) used the Swedish birth register and the Swedish conscript register to determine if a relationship existed between birth weight and adult BMI in 39,901 males. Logistic regression was used to identify the risk of being overweight in young adulthood and odds ratio estimated relative risk. An increase in adult BMI was seen with a birth weight of <2500 grams relating to a BMI of 21.93 kg/m^2 and a birth weight of ≥4500 grams relating to a BMI of 23.02 kg/m^2. Compared to those with a low ponderal index (birth weight in grams/length in cm^3), men with a high ponderal index had an odds ratio for obesity of 1.8 (130).

A study (132) performed using Israeli draft medical examinees was the first to include data on females, although the female population comprised only 39%. Data was used on 33,413 infants born between 1964 and 1971 and followed up at 17 years. A positive association was found in males and females between overweight (BMI ≥90^{th} percentile) and severe overweight (BMI ≥95^{th} percentile) to a birth weight >3000 grams. This association was found when controlling for ethnic origin, parental education level, birth order or area of residence. Additionally, an odds ratio for overweight of 2.16 in males and 2.95 in females with a birth weight ≥4500 grams compared to a birth weight of 3000-3499 grams. No difference was found in BMI between those with a low birth weight (<2500 grams) to those in the reference category (3000-3499 grams) (132).

Two large scales studies have provided information regarding the relationship between birth weight and BMI using data from the United States (19, 22). Information was obtained on 51,289 men using data from the Health Professional Follow-up Study and 71,100 women aged 30-55 years and 92,940 women aged 25-42 years using data from the Nurses' Health Study I and II. In the Health Professional Follow-up Study, a

birth weight of 7.0-8.4 lb (3.2-3.8 kg) was used as the reference category and odds ratios of being in the highest versus the lowest quintile of adult BMI were calculated (19). Those with a birth weight of 8.5-9.9 lb (3.86-4.5 kg) had an odds ratio of 1.5 of being in the highest quintile of adult BMI. In men with a birth weight of over 10 lb (>4.5 kg), the odds ratio of the being in the highest versus lowest quintile of adult BMI was 2.08. However, for men with a birth weight of 5.5-6.9 lb (2.5-3.1 kg), the odds ratio declined to 0.75 (19).

Similar analyses were completed on the data in women using a birth weight of 7.0-8.4 lb (3.2-3.8 kg) as the reference category (22). In those aged 30-55 years with a birth weight 8.6 to 9.9 lbs (3.86-4.5 kg), the odds ratio of being in the highest versus lowest BMI quintile was 1.19 and those with a birth weight >10 lb (≥4.5 kg) had an odds ratio 1.62. Interestingly, a U shape relationship was found between mean BMI and birth weight category where a greater BMI was seen in birth weights below 5 lb and above 7 lb. A J relationship between birth weight and BMI was found in a group of 297 women in East Hertfordshire where an increase in BMI was found with increasing birth weight (P=0.05) (133).

Parsons et al. (27) studied 10,683 male and female infants born in 1958 from Scotland, England and Wales and found a J shape between birth weight and later BMI. Initial birth weight was obtained with follow up data collected at age 7, 11, 16, 23 and 33 years. The relationship between birth weight and BMI was a J shape in both men and women although a linear relationship was found at ages 7, 11 and 16. In males, BMI increased with increasing birth weight in the highest birth weights only (27).

Phillips and Young (136) studied 1750 males and females born between 1920 and 1930 and found with increasing birth weight, BMI in adulthood increased as well. The same results were found in a group of young Swedish women born between 1973 and 1978 (134). A study by Khan et al. (135) also found a linear association between birth weight and BMI (P=0.0004) at age 17-22 years in males who had applied for military service. A final study also examined males only born between 1920 and 1924 in Sweden (138). A weak correlation was found between birth weight and adult BMI at age 50 (r=0.10; P<0.001).

Birth Weight Related to Later Body Mass Index in Children

Several studies have assessed birth weight as a predictor of overweight and risk for overweight in childhood as well (58, 140-146). The importance of obesity development in childhood is highlighted by the statistic that show a child who is obese as an adolescent has an 80% chance of carrying the obesity into adulthood (147).

Birth certificates of participants of the Women, Infant and Children special supplemental food program for low income families in Tennessee were used to obtain weight of infant (140). Birth weight was stratified and compared to weight of child at 3 to 5 years of age. Higher birth weight was directly related to a greater risk of obesity development using a weight for height z score ≥2. The prevalence of obesity in 36-41 month olds with a birth weight of 1000-1499 grams was 1.0% but jumped to 8.7% for a birth weight of 4500-4999 grams (140).

Fisch et al. (141) prospectively collected data in 1,786 Minnesota children relate birth weight to obesity at ages 4 and 7. Birth weight was classified as extremely obese using a body weight score ≥95th percentile. Obesity at birth was directly related to weight

for height >70th percentile at both 4 and 7 years old. Extremely lean children (0 to 5th percentile) and extremely obese children (≥95th percentile) at 4 years tended to remain in their respective classification at 7 years (141). A second prospective longitudinal study in Australia started with an interview of the mother pre-delivery and then followed mother and child for visits immediately after deliver, at 6 months and at 5 years (58). Complete data was obtained on 4,602 subjects and moderate obesity was defined as a BMI between 85th and 94th percentile while severe obesity was defined as BMI >94th percentile. Birth weight was an independent predictor of both moderate and severe obesity and the odds ratio of severe obesity was 1.8 for a birth weight ≥95th percentile (58).

Data from the Study of Children's Activity and Nutrition Project (SCAN) were used to examine the relationship between birth weight and child's BMI at the age of 4 (n=331) (146). This study focuses on determinants of body fatness in Anglo-Americans and Mexican-Americans. Pearson correlations were significant between birth weight and child's BMI (r=0.28; P<0.001) and sum of skinfolds (r=0.16; P<0.01) (146). Research of 1,901 boys and girls aged 7 to 14 years in Germany using cross sectional surveys in 1975, 1985 and 1995 found an association between birth weight and weight in adolescence (142). Using regression and controlling for socio demographic variables, a significant relationship was found between risk of overweight (BMI >90th percentile) and weight at birth in boys (P=0.04) and girls (P=0.035) (142).

Other research studies have been completed but data were collected in developed and often impoverished countries (143-145). In one report, data was obtained from a 25 year longitudinal study in an impoverished Latino village in Guatemala from 1969 to

1977 therefore the applicability to other populations may be limited (143). In 1988 to 1989 a follow up was completed and data was obtained from 1,373 subjects. A positive relationship between weight at 15 days and BMI up to 4 years in girls (r=0.27; $P<0.01$) and up to 5 years (r=0.16; $P<0.0001$) in boys. A second study (144) examined 748 preschool boys and 574 preschool girls in China age 0.1 to 6.9 years. High birth weight ≥4000 grams was identified as a major risk factor for obesity development ($P<0.05$). Bavdekar et al. studied 8 year old Indian children who had participated in an earlier study at the age of 4 years (145). Children with a higher birth weight were heavier at 8 years ($P<0.001$) however, a J shaped relationship was found between birth weight and BMI. At a birth weight of <2.0 kg, this corresponded to a BMI of 13.5 kg/m^2. BMI then declined for those at a birth weight of ≤2.25 kg and ≤2.5 kg; at a birth weight of ≤2.75, BMI climbed back up to 13.5 kg/m^2 and continued to increase linearly ($P<0.001$) (145).

Though the above studies indicate a relationship between birth weight and BMI, a number of studies have found no relationship between these two variables (148-153). Research and study populations in adults finding no relationship include 541 Mexican-American adults (148), 217 middle-aged adults from the United Kingdom (149), 331 postmenopausal Americans (150) and 620 Danish males and females (151). In children, no relationship between birth weight and BMI was found in 7 to 12 year old Americans (n=237) (152) and 9 to 10 year old Italian children (n=110) (153). Possible reasons for discordant findings between studies may be that these studies did not control for sociodemographic factors in analysis, which represents an important determinant of later obesity. Some of these study populations represent low socioeconomic status population and more often low birth weight is common in their children. Research has shown that

obesity decreases with increasing socioeconomic status and thus represents an important confounder factor (154). All of the above mentioned research had study populations below 1,000 therefore they may not have been statistically powered to detect differences that truly existed.

Maternal Obesity and Obesity Development in Offspring

Research has indicated a positive relationship between obesity of the mother and obesity development in the offspring (30, 58, 155-159). Therefore, this indicates obesity in the offspring may be caused by genetics, an adverse intrauterine environment or effects of the postnatal environment such as breastfeeding. In addition to maternal obesity, parental obesity is also related to obesity development in the offspring (58, 157, 158). Thus, this indicates a genetic cause for obesity development in the offspring. A relationship also existed between maternal BMI and birth weight (160, 161).

Data from the Child Health and Development Studies and in the Adolescent Study have provided evidence of the relationship between maternal obesity and obesity development of the offspring (162). Collection of data commenced in 1959 and followed mothers during pregnancy in the San Francisco East Bay area of California. This data was analyzed on 1,993 subjects who had measurements assessed at birth and again at 15, 16 or 17 years. Infants were categorized based on birth weight as small for gestational age ($<10^{th}$ percentile for birth weight), appropriate for gestational age (10^{th} to 90^{th} percentile for birth weight) and large for gestational age ($>90^{th}$ percentile for birth weight). Age specific percentiles of BMI were used to classify mothers. Across each birth weight category there were significant differences in BMI between high maternal BMI and low maternal BMI. High maternal BMI was associated high adolescent BMI.

When the mother was classified with a high BMI, the risk of the obesity development in adolescents was two times those infants who were small or appropriate for gestational age. Additionally, those who were large for gestational age with a mother who had a high BMI had a 5.7 times greater risk of adolescent obesity than those who had lean mothers. Using multiple regression analysis, maternal and parental BMI predicted adolescent obesity, however birth weight was not related (162).

Another large scale longitudinal study has found a relationship between maternal obesity and offspring obesity development at age 7 years (30). The Avon Longitudinal Study of Parents and Children followed children born between 1991 and 1992 in the United Kingdom. The subjects (n=5,493) were brought in for regular exams and obesity was defined as a BMI $\geq 95^{th}$ percentile. Pre-gravid BMI of mother was self reported and was classified as either <30 kg/m^2 or >30 kg/m^2. Adjusted odds ratio for obesity at age 7 years was 4.25 when the mother's BMI was greater than 30 kg/m^2. The odds ratio was adjusted for maternal education, energy intake at 3 years and gender (30).

Li et al. (159) studied 2,636 subjects participating in the 1996 National Longitudinal Survey of Youth, Child and Young Adults in the United States. Height and weight of the children aged 2 to 14 years was measured by trained personnel and overweight was defined as BMI $\geq 95^{th}$ percentile using the Centers for Disease Control growth charts. Maternal pre-gravid BMI was recorded by self report of the mother and categorized as overweight (25 kg/m^2 $\leq$ BMI <30 kg/m^2) and obese (≥ 30 kg/m^2). A linear trend between maternal pre-gravid BMI and increased risk of overweight in childhood was found ($P<0.001$). Children were at a 4 times greater risk of overweight in

adolescence if their mothers were obese compared to those children whose mothers had a normal BMI (159).

Using data from the National Collaborative Perinatal Project and the Philadelphia Blood Pressure Project, risk for increased adiposity in adulthood in African Americans was assessed (163). A total of 447 subjects participated who had a recorded birth weight and follow up data at age 18-23 years. At follow up, sum of 2 skinfold thickness were assessed on the offspring. When subjects were enrolled in the study, maternal pre-pregnancy weight was recorded by self report and maternal obesity was defined as BMI $\geq$30 kg/m^2. Using multiple logistic regression, three factors were related to increased adiposity; maternal pre-gravid BMI, female gender and first born status. An odds ratio of 1.15 was found for each kg/m^2 increment increase in maternal pre-pregnancy BMI (P=0.001) (163).

Data from the 1958 British birth cohort indicated a relationship between maternal BMI and offspring adiposity (27). A J shape relationship was found however after adjusting for self report of mother's pre-pregnancy weight, this relationship disappeared. The Nurses' Health Study was also used to examine this relationship with 71,100 participants (22). Data indicated a relationship between maternal BMI and obesity in adulthood however maternal body weight was assessed by identification of a closely resembling image of their mother's body shape at age 50 years.

Other research has found a relationship between birth weight and future obesity in the offspring however independent of pre-gravid BMI (164-166). Duran-Tauleria et al. (164) performed a cross sectional analysis consisting of 8,374 children who had participated in an earlier study providing birth weight and parental BMI. Researchers

measured weight and skinfold thickness in the children aged 5 to 11 years. Multivariate analysis found, independent of parental or maternal BMI, age and gender adjusted weight for height scores significantly related. Further research (165) in 1,363 children from Italy found associations between risk of obesity and birth weight ($P<0.01$) and parental or maternal BMI ($P<0.001$). However, using multiple logistic regression, the association between obesity and birth weight remained independent of maternal or parental BMI. Gallaher et al. (166) conducted a medical review of 261 preschool children from the Mescalero Apache tribe. Children with an obese mother were two times more likely to be obese than those with non obese mothers. Similarly, children with a high birth weight (>4000 grams) were three times more likely to be obese compared to a birth weight of 2000 to 2999 grams. Both of these results were after adjusting for age, gender and maternal obesity.

Explanations for the discrepancies in results may lie in the fact that the effect of birth weight on weight for height diminishes with age (164). Additionally, the findings may be an artifact reflecting the accuracy of the assessment of birth weight and maternal BMI. In nearly all studies, an accurate measure was obtained for birth weight either through medical records or by the investigator however, maternal BMI was usually self reported by the mother. This could result in the true relationship between obesity development in the offspring and maternal BMI being underestimated.

Relationship of Maternal Pre-Gravid BMI to Offspring Body Composition

Few studies have attempted to assess infant body composition in relation to maternal factors (59, 167). Furthermore, special populations such as infants could potentially violate the underlying assumptions of the multi-component models therefore;

the accuracy of the technique depends on the model and the associated assumptions. When assessing body composition in infants, special consideration must be taken into account when selecting a technique and caution must be used when examining the results.

Assessment of infant body composition is often not feasible and routinely BMI or the ponderal index is used to quantify infant risk of overweight. Of the studies that have examined infant body composition in relation to maternal factors, the impact of diabetes during pregnancy is often compared to those without diabetes. Catalano et al., (167) assessed infant body composition using skinfold measurements from 195 mothers who had gestational diabetes and compared this to body composition from 220 infants born to mothers with normal glucose tolerance. No differences between groups were found for birth weight or fat-free mass however infants from mothers with gestational diabetes had greater skinfold measurements and fat mass. Furthermore, fasting glucose levels were had the greatest correlation with infant body fat (167).

One study has assessed infant body fat and compared this by pre-gravid BMI of the mother by dividing into this two categories: normal (<25 kg/m^2) and overweight/obese (≥25 kg/m^2). Sewell et al. (59) compared body composition of infants using TOBEC from mothers who were overweight/obese (≥25 kg/m^2) and mothers who were normal (<25 kg/m^2). All subjects were tested and classified as normal glucose tolerant based on results of an oral glucose tolerance test. Those with positive screen for gestational diabetes were excluded from analysis. Within 72 hours of delivery, infant body composition was tested (59).

A total of 76 (34 female and 42 male) infants were from overweight/obese mothers and 144 (67 female and 77 male) were from normal pregnancies (59). Infants from mothers who were overweight/obese had greater body fat (11.6 %fat versus 9.7 %fat; *P*=0.03) and fat mass (420 g versus 380 g; *P*=0.01). Birth weight approached significance (P=0.051) (3284 g versus 3436 g) with overweight/obese women infants weighing more at birth. Linear regression was used to assess the impact of weight gain during pregnancy on infant body composition measures. In the normal group, fat-free mass was associated with weight gain while in the overweight/obese group, infant body fat was associated to weight gain during pregnancy (59). Multiple stepwise regression was used to examine which factors contributed to the prediction of infant body composition measures. In normal mothers, gestational age and fetal gender explained 20% of infant body fat while fat-free mass was explained by gestational age and maternal weight gain. In the overweight/obese group, infant body fat was explained by weight gain, gestational diabetes screen and gestational age with gestational age and weight gain contributing the most. Furthermore, in the overweight/obese group fat-free mass was explained by gestational age, gender and nulliparity with gestational age contributing the most (59).

Sewell et al. found the differences between groups were attributed to increases in fat mass and not fat-free mass. This is the first study to compare pre-gravid BMI of the mother to infant body composition. Other studies (168) have compared pre-gravid BMI to infant birth weight and found a positive relationship, but they failed to assess which component of birth weight (fat mass versus fat-free mass) was responsible for the

difference. Thus, women who are overweight/obese when compared to normal women, had infants with greater body fat and fat mass (59).

CHAPTER III

METHODS

The purpose of this study was to compare infant body weight and composition from mothers who were categorized as normal (<25 kg/m^2) or overweight/obese (≥25 kg/m^2) pre-gravid body mass index (BMI).

Subjects

The study sample consisted of 72 full-term infants and their mothers recruited from Oklahoma City, Oklahoma and surrounding areas, who were healthy full-term infants ≤35 days old. Eligibility for participation included the following criteria at baseline: 1) healthy male or female full-term infant with a gestational age of ≥37 weeks and ≤42 weeks and 2) mothers at the time of delivery between the ages of 18 to 45 years. Exclusion criteria for the study included: 1) infants with a prolonged medical stay defined as >3 days, 2) tobacco use during pregnancy, 3) excess alcohol consumption during pregnancy defined as >1 drink a week, 4) infants with presumed or known chromosomal or severe congenital abnormalities, and 5) infants from mothers with type 1, type 2 or gestational diabetes.

Two groups of subjects were recruited: 1) 33 infants born to mothers with a pre-gravid BMI of <25 kg/m^2 and 2) 39 infants born to mothers with a pre-gravid BMI of ≥25 kg/m^2.

Study Design

This research study used a cross-sectional study design. Subjects were required to participate in one visit, during the visit, body weight, length and body composition were assessed in the infant. In addition, mother's height and weight were measured.

Procedures

Participants were recruited by a mass email sent to the University of Oklahoma Health Sciences Center, newspapers advertisements, announcements in birthing classes, and flyers placed at various pediatric clinics throughout the greater Oklahoma City area. All testing occurred in Children's Hospital in Oklahoma City. The testing procedure began with an orientation where the entire testing procedure was explained along with all risks and benefits of participation. Once all questions were answered, an informed consent and HIPAA form was signed and copies of the signed documents were given to the participants. Air-displacement plethysmography (i.e. Pea Pod®) was used to assess body volume of the infant while naked in the Pea Pod®. This study was approved by the Institutional Review Board for Human Participants at the University of Oklahoma Health Sciences.

Body Weight

Body weight of the infant was obtained using the Pea Pod® scale. To assess body weight, the infant's clothing and diaper was removed. The infant was placed naked on the scale and a body weight was obtained to the nearest 0.01 kg. Body weight of the mother was obtained with shoes removed and in minimal clothing. A physician's balance beam scale was used to measure body weight in kilograms to the nearest 0.1 kg.

Height

Height of the mother was obtained using a stadiometer (Accu-Hite Wall Stadiometer, Seca Corp., Hanover, MD). She removed her shoes, was centered on the stadiometer and placed her hands on hips. After an inhalation, height was measured to the nearest 0.1 centimeter.

Length

Crown to heel length of the infant was assessed using a length board. The infant was placed on their back with their head against the immovable piece of the stadiometer and their legs placed toward the adjustable end of the stadiometer. Next the infant was stretched out so their head remains stable but their legs are extended. At the point where their legs are extended, the adjustable portion of the stadiometer was moved so that it is flat against their outstretched feet. A reading was taken and recorded to the nearest 0.1 centimeter.

Air Displacement Plethysmography by the Pea Pod®

The Pea Pod® Body Composition System (Life Measurement Instruments, Concord, CA) was used to assess body volume and used to calculate body density. The Pea Pod® was calibrated before each test or once daily during testing days when multiple tests were performed. A calibration cylinder with a known volume was used to calibrate the chamber and a 5000 gram weight was used to calibrate the scale.

When testing takes place, the infants were naked, with all clothing and diaper removed. Weight of the infant was obtained prior to start of the measurement. After body weight was measured, the infant was placed inside the Pea Pod® and a body volume measurement was completed. Assessment of the body volume lasted approximately 2 minutes and once body volume was obtained, the test was complete. Body density was then converted to percentage of fat (%fat) using gender specific equations by Foman (169).

The concept of air displacement plethysmography (ADP) is not new, but only within the last 10 years has it been made commercially available for body composition

testing (60). The first product utilizing ADP was a version used to test adolescents and adults. Recently, an infant version has been made available (75) and holds promise to provide a method for a fast and accurate method to assess body composition in infants.

ADP involves assessment of body density by measurement of body volume (75). A two-compartment approach to body composition is then applied in which body density is used to calculate percent body fat (% fat), fat mass and fat-free mass (61). Body density equals body volume divided by body weight. Assessing body weight in air is achieved by using a scale.

Application of basic gas laws allow for body composition assessed by ADP based on the relationship between pressure and volume (60, 75). Boyle's law states at constant (isothermal) temperature, pressure and volume are inversely related:

$$P_1/P_2=V_2/V_1$$

where P_1 and V_1 are pressure and volume at an initial state and P_2 and V_2 are pressure and volume at a final state. Air inside the test chamber is however, under adiabatic conditions (occurring with loss of heat). Therefore the air inside the chamber does not remain constant as volume changes and as molecules gain or lose kinetic energy. Thus, Poisson's Law describes the relationship used by ADP under adiabatic conditions (60, 75) and is described using the following equation:

$$P_1/P_2 = (V_2/V_1)^{\gamma}$$

where γ represents a constant (1.4) for air. Equations 1 and 2, illustrate that volume changes result in different pressure changes for air under adiabatic and isothermal conditions. Air under isothermal conditions is more easily compressed than air under

adiabatic conditions and therefore air under adiabatic conditions will be overestimate by 40% (60).

The Pea Pod® is mounted entirely on a cart to allow ease of movement to testing locations. The testing chamber, reference chamber, calibration volume, electronics, and scale are all based on the cart. Between the test and reference chamber is a volume perturbing diaphragm and a pneumatic calibration valve connects the test and calibration volume. The scale is mounted on the surface of the unit to assess weight using a strain gauge and the scale has a capacity of 12 kg (75).

During testing, oscillations in the diaphragm create sinusoidal volume perturbations in the test and reference chamber (75). The volume perturbations operate at a magnitude and frequency of 35 mL and 6 Hz, respectively. Changes in pressure resulting from volume perturbations are below ±0.5 cm H_20 and maintained low for comfort. For a known volume in the reference chamber under adiabatic conditions, changes in the test chamber are a linear function of the ratio of the pressure perturbations between the test and reference chambers (75). Due to the compressible nature of isothermal air, these volumes must be corrected. Therefore, during testing sources of isothermal air, such as air close to the skin, in the hair and air in the lungs must be taken into account. Failing to account for isothermal air in the testing chamber would result in a 40% overestimation of volume behaving isothermally when adiabatic conditions are assumed. To correct volume estimates, the surface area artifact (SAA) was calculated (75). During volume measurements, the Pea Pod computer software calculated body surface area (BSA) and multiplied it by a constant (k) to obtain SAA using the following equations:

$$BSA\ (cm^2) = 178.27 * length\ (cm)^{0.5} * weight\ (kg)^{0.4838}$$

$$SAA\ (L) = k(L/cm^2) * BSA\ (cm^2)$$

Due to isothermal air in the lungs, where adiabatic conditions are assumed, air in lungs is overestimated by 40% resulting in the body volume of the subject being underestimated by 40% of the subject's thoracic gas volume (TGV) (75). To correct this, TGV is estimated and 40% of the estimated TGV is added back to the measured value of the subject's body volume. Direct assessment of TGV is not feasible in infants so it is predicted.

TGV= Functional residual capacity (FRC) + ½ Tidal volume (TV)

FRC can be assessed by helium dilution or plethysmographic assessment. However helium dilution results in lower values of FRC due to trapped air in the lungs undetectable by helium dilution (170). The Pea Pod® uses a plethysmographis derived equation to calculate FRC shown below (171):

$$FRC\ (mL) = 2.36 * length\ (cm)^{0.75} * weight\ (kg)^{0.63}$$

TV values depend on age and mass of the infant and are equal to 7 ml/kg at birth, 9 ml/kg at 3 months, 9.3 ml/kg at 6 months and 9.5 mL/kg at 12 months (172).

TGV is then calculated based on the following formula:

$$TGV = FRC + ½\ TV$$

These values are used to calculate raw body volume (BVraw) and body volume (BV):

$$BV\ (L) = BVraw - SAA\ (L) + 40\%\ TGV\ (L)$$

The remaining factor needed to calculate body density and %fat are body mass of the subject (Mb):

$$Mb/Db = Mf/Df\ +\ Mfm/Dfm$$

$$\%fat = (Mf/Mb) * 100\%$$

where Mf is fat mass, Df is fat density, Mffm is fat-free mass (equal to Mb – Mf) and Dffm is density of fat-free mass. A known value for Df equal to 0.9007 g/mL (61) is used in the equation. However, age and sex specific Dffm values must be used and are presented elsewhere (169).

Prior to the start of testing, volume calibration was completed using a phantom of known volume and every two weeks or when the device has been moved, the scale is calibrated using an NIST-traceable calibration weight (5000 grams) (75). Once the device is calibrated, the test procedure begins with a simultaneous body mass measurement and an automated volume calibration. While the test chamber is empty, changes in pressure are assessed with the calibration open and closed. A two point calibration is completed with the closing and opening of the calibration valves. This procedure lasts less than a minute and upon completion the test chamber is ready for placement of the infant inside the tray for body volume assessment (75).

The tray and the infant were pushed inside the device and the door is shut to start the assessment. Within the first 15 seconds of the test, air outside the test chamber is allowed to mix with air inside the test chamber avoiding temperature dependent deformations in the walls of the test chamber due to the generation of heat by the infant (75). Over the next 25 seconds, pressure changes occurring between the test and reference chamber are recorded. Two volume measurements are obtained and if they are within 5 mL of each other, then the mean is used to determine %fat. If the volume measurement fails, a third is taken and the mean of the two within agreement are used to

calculate %fat. When three measurements are not in agreement, then the test must be repeated (75).

Statistical Analysis

Descriptive statistics (means and standard deviations) were calculated for all outcome variables (birth weight, %fat, total fat mass and fat-free mass) within both of the two groups according to mother's pre-gravid BMI status. The two groups were compared to determine if any differences existed between them. For interval data, independent t-tests were used and for nominal data a chi-square test was completed.

To determine whether birth weight and body composition, adjusted for infant age at visit, differed based on pre-gravid BMI (2 levels: normal and overweight/obese), analysis of covariance (ANCOVA) was performed. Stepwise multiple linear regression analysis determined which maternal factors were related to infant outcome variables. The dependent variables used in the model were: neonate birth weight, %fat, fat mass and fat-free mass; independent variables were gestational age, infant age at testing, maternal pre-gravid body weight, BMI, maximum body weight, weight gain, gender and socioeconomic status. The alpha level was set at $P \leq 0.05$.

Power/Sample Size Considerations

Cohen's *d* (173) was calculated using the following formula:

$$d = \frac{M_1 - M_2}{\sqrt{SD_1 + SD_2}/2}$$

where '*d*' is the expected mean difference between any two groups and *'SD'* is the standard deviation for individual measurements. Once '*d*' was calculated, a power table was used to determine the estimated sample size. The mean difference in infant birth weight between overweight/obese mothers and normal weight mothers was 2.0 ± 2.5

%fat (59, 174). A significance level of 0.05 and 80% statistical power were used to estimate sample size as shown in Table 2.

Table 2. Sample size determination.

Groups	*d*	*sd*	N (estimated sample size)
	Percent Body Fat (%fat)		
Overweight/obese vs. Normal	2.0	2.5	26

(*d*: mean difference; *sd*: standard deviation)

Since the calculated sample size per group was 26 subjects, we anticipated a possible non-compliance rate of 25%, we considered a total sample size of 66 (33 subjects per group) to be adequate.

CHAPTER IV

MANUSCRIPT

IMPACT OF MATERNAL BODY MASS INDEX ON NEONATE BIRTH WEIGHT AND BODY COMPOSITION

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Objective: The purpose of this study was to compare body weight and composition (%fat, fat mass, and fat-free mass) in neonates born to mothers with a normal pre-gravid body mass index (BMI; <25 kg/m^2) versus neonates born to mothers with an overweight/obese pre-gravid BMI (≥25 kg/m^2).

Study Design: Seventy-two neonates (33 from normal mothers and 39 from overweight/obese mothers) of singleton pregnancies with normal glucose tolerance had their body weight and body composition assessed by air-displacement plethysmography.

Results: After controlling for neonate age at time of testing, significant differences were found between groups for %fat (12.5 ± 4.2 % vs. 13.6 ± 4.3 %; $P \leq 0.0001$), fat mass (414.1 ± 264.2 g vs. 448.3 ± 262.2 g; $P \leq 0.05$) and fat-free mass (3310.5 ± 344.6 g vs. 3162.2 ± 343.4 g; $P \leq 0.05$), with no significant differences between birth length (50.7 ± 2.6 cm vs. 49.6 ± 2.6 cm; $P = 0.08$) or birth weight (3433.0 ± 396.3 g vs. 3368.0 ± 399.6 g; $P = 0.44$).

Conclusions: Neonates born to mothers who have a normal BMI have significantly less total and relative fat, and more fat-free mass than neonates born to overweight/obese mothers. Though preliminary, these data suggest that the antecedents of future disease risk (e.g. cardiovascular disease, diabetes, and obesity) occur early in life.

Background

Maternal prenatal obesity has increased significantly over the past 15 years with maternal body weight at the first prenatal visit increasing by 20% (39, 175). At the same time, neonate birth weight in North America and Europe has increased, with birth weight >90th percentile and >4000 grams increasing the most (40, 41). A body of work has emerged to show a positive relationship between maternal body mass index (BMI) and the birth weight of their off-spring (28, 176-178), with newborns at a birth weight ≥90th percentile possessing the greatest risk of obesity later in adulthood (21, 130, 137, 139).

Intrauterine life is a crucial period with epidemiologic data indicating that a sub-optimal intrauterine environment affects future chronic diseases (179, 180). Barker has proposed that prenatal factors that alter or impede fetal growth in utero may have long-term ramifications and may be in part responsible for obesity (181), diabetes (182), hypertension (183), insulin resistance (184), cardiovascular (179), and heart disease (97, 179, 185-187). Barker coined the hypothesis "the fetal origin hypothesis", which refers to the induction, deletion, or impairment of fetal growth by an early event in utero that alters fetal tissue on a molecular or physiological level (15, 16).

The intrauterine environment is assessed crudely by birth weight of the infant. However, birth weight is not the sole indicator of intrauterine nutritional status (17). For instance, low birth weight caused by under nutrition during gestation is defined as a birth weight below 2500 grams or <10th percentile (18). However, birth weight does not distinguish the impact of poor maternal nutrition or whether infants failed to thrive (17).

Even though some research suggests a relationship between birth weight and development of disease in adulthood, the relationship remains equivocal (31-35). Other

research (32) suggests inadequate nutrition during pregnancy may affect health in adulthood indirectly. Consequently, the influence of birth weight on adult health is paradoxical; both low and high birth weight are associated with increased incidences of adult disease such as diabetes (13, 167, 184). To address these divergent views regarding the relationship between an adverse intrauterine environment, we designed a study to delineate the association between maternal weight and neonate birth weight and body composition. Therefore, the purpose of this study was to compare infant body weight and composition from mothers who had a normal pre-gravid BMI (<25 kg/m^2) or whom had an overweight/obese pre-gravid BMI (≥ 25 kg/m^2).

Research Methods and Procedures

Participants

Participants were recruited by mass emails sent to the University of Oklahoma Health Sciences Center, newspapers advertisements, announcements in birthing classes and flyers placed at pediatric clinics in the Oklahoma City area. Testing occurred in Children's Hospital in Oklahoma City. This study was approved by the Institutional Review Board for Human Participants at the University of Oklahoma Health Sciences. All participants signed an informed consent and HIPPA prior to testing.

Participants included mothers and their infants who were healthy full-term infants $\leq$35 days old. Inclusion criteria were: 1) healthy infants, defined as spending <3 days in the hospital after delivery, 2) gestational age $\geq$37 weeks and <42 weeks and, 3) age of mother at the time of delivery between the ages of 18 to 45 years. Exclusion criteria for the study included the following: 1) any tobacco use during pregnancy, 2) excess alcohol consumption during pregnancy defined as >1 drink a week, 3) infants

with presumed or known chromosomal or severe congenital abnormalities, and 4) infants of mothers with diabetes (i.e. type 1, type 2 or gestational diabetes).

Maternal body weight before pregnancy, weight gain during pregnancy, total family income and maximum weight reached during pregnancy were obtained by interview during the consenting process, which occurred at the time of neonate testing. Neonate birth weight and birth length were also self-reported by the mother. The mother's pre-gravid BMI was calculated using the participants self-reported body weight prior to pregnancy and their height was measured at the visit.

Air-displacement Plethysmography (PEA POD®)

Infant length was measured using a length board. Infants were stretched out so that his/her head remained stable but his/her legs were extended. The adjustable portion of the stadiometer was placed against their outstretched feet. Length was recorded to the nearest 0.1 centimeter. The Pea Pod® Body Composition System (Life Measurement Instruments, Concord, CA) was used to measure body weight and body volume. The Pea Pod® was calibrated before each test or once daily during testing days where multiple tests were performed. A calibration cylinder with a known volume was used to calibrate the chamber and a 5000 gram weight was used to calibrate the scale. Testing procedures have been described in detail elsewhere (75). To assess body weight, the infant's clothing and diaper were removed. The infant was placed naked on the scale and a body weight was obtained to the nearest 0.0001 kg. After body weight was measured, the infant was placed inside the Pea Pod® wearing a wig cap and a body volume measurement was performed. Assessment of the body volume required approximately 2 minutes. Body density was then converted to percentage of fat (%fat) using gender

specific equations by Foman (169). At the completion of testing, body composition variables were then calculated; relative fat (%fat), total fat mass, and fat-free mass.

Maternal Weight and Height

Mothers removed all loose fitting clothing and shoes before being weighed on a physician's balance beam scale (Detecto Scales, Webb City, MO) to the nearest 0.1 kg. Height of the mother was obtained using a stadiometer (Accu-Hite Wall Stadiometer, Seca Corp., Hanover, MD). Participants removed their shoes and centered their feet on the stadiometer with their hands placed on her hips. After an inhalation, height was measured to the nearest 0.1 centimeter.

Statistical Analyses

Descriptive statistics (means and standard deviations) were calculated for all outcome variables (birth weight, %fat, total fat mass and fat-free mass) within both of the two groups according to mother's pre-gravid BMI status. The groups were compared to determine if any differences existed between the two groups. For interval data, independent t-tests were calculated and for nominal data, a chi-square test was completed.

To determine whether birth weight and body composition, adjusted for infant age at visit, differed based on pre-gravid BMI (2 levels: normal and overweight/obese), analysis of covariance (ANCOVA) was performed. Stepwise multiple linear regression analysis determined which maternal factors were related to infant outcome variables. The dependent variables used in the model were: neonate birth weight, %fat, fat mass and fat-free mass; independent variables were gestational age, infant age at testing,

maternal pre-gravid body weight, BMI, maximum body weight, weight gain, gender and socioeconomic status. The alpha level was set at $P \leq 0.05$.

Results

Seventy-two women (33 with a normal pre-gravid BMI (<25 kg/m^2) and 39 with an overweight/obese (≥25 kg/m^2) pre-gravid BMI) enrolled in the study. The majority of the sample was Caucasian (80%), with the remainder comprised of African American (3%), Native American (4%), Asian (1%), Hispanic (6%) with the remaining 6% classifying themselves as other races.

The groups did not significantly differ in age, height, weight gain during pregnancy, gender of infant, status of feeding (breast vs. formula), or family income (Table 1). Pre-gravid body weight, BMI, maximum weight during pregnancy, and body weight at the time of visit were significantly different between the two groups (Table 1).

Infants of mothers with a normal pre-gravid BMI had a greater gestational age and birth length than infants from overweight/obese mothers $P \leq 0.05$ (Table 2). ANCOVA controlled for maternal factors that potentially affect fetal growth and subsequent neonate body weight and composition. Covariates investigated were gestational age, infant age at testing, maternal pre-gravid body weight and BMI, maximum body weight, weight gain, gender, and socioeconomic status. Only neonate age at testing was significant. Therefore, anthropometric variables body weight and composition data for infants from both the normal and overweight/obese groups were adjusted for infant age at testing (Table 2). The groups did not differ for birth weight or length, however differences between groups were found in infant body composition variables. Offspring of the normal group had lower body fat and fat mass and greater fat-

free mass than offspring of mothers who were overweight/obese (Table 2). Unadjusted means for infant outcome variables are listed in Appendix D.

Multiple stepwise regression analysis assessed the relationship between maternal factors to infant body weight and composition in the normal (Table 3) and overweight/obese (Table 4) groups. We examined the two groups using separate stepwise approaches entering gestational age, infant age at testing, maternal pre-gravid body weight, BMI, maximum body weight, weight gain, gender, and socioeconomic status as independent predictor variables. We examined separate models for each of the four dependent variables: birth weight, %fat, fat mass, and fat-free mass as dependent variables. In the analysis of birth weight, no significant correlations existed with any of the independent predictor variables for either group. In the analysis of %fat for both the normal and overweight/obese groups, the only significant association was with infant age at testing (Tables 3 and 4). Lastly in the analysis, fat-free mass in the normal group was associated with infant gender (Table 3). In the overweight/obese group, fat-free mass was associated with feeding status, infant age at visit, and gestational age (Table 4).

Discussion

The primary purpose of this study was to better understand the impact of maternal BMI on infant birth weight and body composition. Our main findings were that infants born to mothers with a normal pre-gravid BMI had less fat mass and greater fat-free mass than infants born to mothers who were overweight/obese.

Our study showed no difference in birth weight between groups. However, numerous studies have reported maternal BMI and neonate birth weight having a

positive linear relationship (28, 59, 160, 168, 176-178, 188-190). This association has been shown in European samples as well. In an Austrian sample of 10,240 singleton births, Kirchengast et al. (177) reported a positive relationship between pre-pregnancy BMI and birth weight and in a Swedish sample Rossner and Ohlin (168) reported that maternal weight gain and initial maternal body weight predicted infant birth weight. The consensus in all of these studies clearly demonstrates a strong positive relationship between maternal BMI and birth weight.

Our data showed no significant difference in birth weight between the two groups; however, neonates from mothers with a normal pre-gravid BMI had significantly less %fat, total fat mass, and more fat-free mass than neonates from overweight/obese mothers. Similar results were reported by Sewell et al. (59) who showed no significant difference in birth weight in offspring from mothers with a pre-gravid BMI <25 kg/m^2 and a pre-gravid BMI ≥ 25 kg/m^2. Their body composition data (determined by total body electrical conductivity) revealed a significantly greater amount of fat mass and %fat in the neonates from overweight/obese mothers though no difference in fat-free mass was found. They concluded pre-gravid obesity played a significant role in infant fat mass, but interestingly, not in fat-free mass (59).

To further refine the relationship between body composition and maternal BMI, we performed multiple stepwise regression to determine which independent variables were associated with the increased total fat mass and decreased fat-free mass in the neonates born to mothers who were overweight/obese. In neonates from overweight/obese mothers, the variable that explained the most variability in %fat was the infant's age at the time of the visit. Infant age at visit in our study ranged from 5 days

up to 35 days while all testing for Sewell's population occurred within 72 hours of birth (59). It is unclear if they used infant age at the time of testing as an independent variable.

We also developed a model to examine which factors predicted fat-free mass. In infants from normal mothers, infant gender was highly related to fat-free mass accounting for 23% of the variance between the two variables. However, in overweight/obese infants, the greatest predictors of fat-free mass were feeding status (breast versus formula), infant age at visit and gestational age. This model accounted for 42% of the variance in fat-free mass.

Despite compelling epidemiological data, vigorous debate disputes the veracity of the fetal origin hypothesis and its linking of maternal weight, neonate birth and future disease risk (59, 191) (192). Generally speaking, it is accepted that maternal weight is associated with birth weight (193), and evidence shows that the incidence of neonates weighing >4,000 grams increases as mothers BMI increases from normal (8%) to morbidly obese (15%) (194).

Perhaps the fetal origins hypothesis and the relationship between maternal weight and their offspring is obfuscated because of a lack of accurate assessment tools available to assess confounding variables, namely fat mass and fat-free mass. It is our theory that fat mass and fat-free mass (lack there of) at birth, rather than body weight *per se*, is what mediates the adult consequences of variations in fetal growth.

The implementation of body composition assessment in neonates is rare, partly because of a lack of valid instruments. However, elegant work by Catalano (195) and Sewell (59) has shown that 83% of the variability in birth weight is explained by fat-free mass. For this reason that our study findings are unique and novel, because we studied

not only birth weight but also body composition. However, more studies that use body composition are needed to fully understand the role maternal weight plays on neonate weight and the subsequent risk of future chronic diseases.

Future work is needed to expand our understanding of maternal pre-gravid weight on infant outcomes. It would be ideal to assess maternal body composition prior to or during pregnancy to clearly delineate the role of maternal nutrition on metabolic disturbances in the offspring. Research has shown that in cases of gestational diabetes or impaired glucose tolerance, the fetus is exposed to increased levels of nutrients resulting in hyperglycemia, hyperinsulinemia. These exposures increase the risk of obesity in childhood and adulthood (196). Furthermore, detailed and careful nutrient intake and physical activity levels are needed to discern specific associations with the intent of establishing cause and effect relationships. Rat models have shown that a diet high in saturated fat during gestation resulted in offspring with abnormal vascular function and altered plasma lipid and fatty acid content (52).

In conclusion, infants born to overweight/obese mothers had a greater %fat and fat mass and less fat-free mass than infants from mothers with a normal BMI. Though provocative, further work taking a panoptic view is needed. This would be particularly important for understanding the impact of maternal diet on neonate body weight and composition.

Acknowledgements

We are indebted to the participants of this study. Additionally, we would like to acknowledge Lauren Pratt for her work in coordinating participant visits and in data collection. We would also like to thank Joel Cramer, PhD for his help in data analysis

and interpretation. This study was funded in part by a College of Medicine Alumni Association grant (University of Oklahoma Health Sciences Center).

Table 1: Maternal demographics of the normal (<25 kg/m^2) and overweight/obese groups (≥25 kg/m^2).

	Normal (N=33)	**Overweight/ Obese (N=39)**	***P* Value**
Age at delivery (yrs)	27.9 ± 5.3	28.0 ± 5.6	0.94
Pre-gravid body weight (kg)[†]	58.9 ± 6.7	87.0 ± 21.6	0.000
Pre-gravid BMI (kg/m^2)[†]	21.7 ± 1.9	31.8 ± 6.9	0.000
Maximum weight during pregnancy[†]	73.5 ± 8.3	98.5 ± 20.4	0.000
Weight gained during pregnancy[†]	14.8 ± 4.3	13.0 ± 4.7	0.82
Body weight at visit (kg)	66.1 ± 8.4	92.4 ± 22.4	0.000
Height at visit (cm)	164.5 ± 5.3	164.9 ± 7.0	0.75
Income (%)			0.32
<$30,000	27%	46%	
$30,001 to $60,000	31%	22%	
$60,001 to $90,000	18%	8%	
>$90,000	24%	24%	

Mean ± standard deviation

[†]Self report by the mother

Table 2: Demographics and neonate outcome variables of neonates from normal (<25 kg/m^2) and overweight/obese study groups (≥25 kg/m^2). Differences are based on results of analysis of covariance and means of infant outcome variables were adjusted for infant age at visit.

	Normal (N=33)	**Overweight/ Obese (N=39)**	***P* Value**
Male gender (%)	42%	44%	0.56
Breast fed (%)	79%	72%	0.40
Gestational age (weeks)[†]	39.5 ± 1.2	38.9 ± 1.0	0.03
Infant age at time of testing (days)[†]	19.5 ± 8.5	19.8 ± 9.3	0.91
Infant Out Come Variables			
Birth length (cm)[†]	50.7 ± 2.6	49.6 ± 2.6	0.08
Birth weight (g)[†]	3433.0 ± 396.3	3368.0 ± 399.6	0.44
%fat	12.5 ± 4.2	13.6 ± 4.3	0.000
Fat mass (g)	414.1 ± 264.2	448.3 ± 262.2	0.04
Fat-free mass (g)	3310.5 ± 344.6	3162.2 ± 343.4	0.03

Mean ± standard deviation

[†]Self report by the mother

Table 3: Multiple stepwise regression analysis for factors that affected infant outcome variables in 33 women with a pre-gravid BMI <25 kg/m^2.

Factor	r^2	Δr^2	*P* Value
%fat			
Infant age at visit	0.29	-	0.003
Fat-free mass			
Infant gender	0.23	-	0.000

Table 4: Multiple stepwise regression analysis for factors that affected infant outcome variables in 39 women with pre-gravid BMI ≥25 kg/m^2.

Factor	r^2	Δr^2	*P* Value
%fat			
Infant age at visit	0.28	-	0.000
Fat-free mass			
Feeding status	0.22	-	0.007
Infant age at visit	0.31	0.09	0.007
Gestational age	0.42	0.11	0.021

REFERENCES

1. Hedley AA, Ogden CL, Johnson CL, et al. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *Jama.* 2004;291:2847-50.
2. Grundy SM, Brewer HB, Jr., Cleeman JI, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation.* 2004;109:433-8.
3. Mei Z, Scanlon KS, Grummer-Strawn LM, et al. Increasing prevalence of overweight among US low-income preschool children: the Centers for Disease Control and Prevention pediatric nutrition surveillance, 1983 to 1995. *Pediatrics.* 1998;101:E12.
4. Morrison JA, Barton BA, Biro FM, et al. Overweight, fat patterning, and cardiovascular disease risk factors in black and white boys. *J Pediatr.* 1999;135:451-7.
5. Daniels SR, Morrison JA, Sprecher DL, et al. Association of body fat distribution and cardiovascular risk factors in children and adolescents. *Circulation.* 1999;99:541-5.
6. Klein DJ, Aronson Friedman L, Harlan WR, et al. Obesity and the development of insulin resistance and impaired fasting glucose in black and white adolescent girls: a longitudinal study. *Diabetes Care.* 2004;27:378-83.
7. Cook S, Weitzman M, Auinger P, et al. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med.* 2003;157:821-7.
8. Hillier TA and Pedula KL. Complications in Young Adults with Early-Onset Type 2 Diabetes. *Diabetes Care.* 2003;26:2999-3005.
9. Allison DB, Fontaine KR, Manson JE, et al. Annual Deaths Attributable to Obesity in the United States. *JAMA.* 1999;282:1530-1538.
10. *National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2000*. 2002, US Dept of Health and Human Services, Centers for Disease Control and Prevention: Atlanta, Ga.

11. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med.* 2005;352:1138-45.
12. Fontaine KR, Redden DT, Wang C, et al. Years of life lost due to obesity. *JAMA.* 2003;289:187-193.
13. Dietz WH. Critical periods in childhood for the development of obesity. *Am J Clin Nutr.* 1994;59:955-9.
14. Barker DJ. Fetal origins of coronary heart disease. *BMJ.* 1995;311:171-4.
15. Hales CN and Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia.* 1992;35:595-601.
16. Lucas A. Programming by early nutrition in man. *Ciba Found Symp.* 1991;156:38-50; discussion 50-5.
17. McMillen IC and Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev.* 2005;85:571-633.
18. Bernstein I. Fetal body composition. *Curr Opin Clin Nutr Metab Care.* 2005;8:613-7.
19. Curhan GC, Willett WC, Rimm EB, et al. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation.* 1996;94:3246-50.
20. Gillman MW, Rifas-Shiman S, Berkey CS, et al. Maternal gestational diabetes, birth weight and adolescent obesity. *Pediatrics.* 2003;111:221-226.
21. Rasmussen F and Johansson M. The relation of weight, length and ponderal index at birth to body mass index and overweight among 18-year-old males in Sweden. *Eur J Epidemiol.* 1998;14:373-80.
22. Curhan GC, Chertow GM, Willett WC, et al. Birth weight and adult hypertension and obesity in women. *Circulation.* 1996;94:1310-5.
23. Bazaes RA, Alegria A, Pittaluga E, et al. Determinants of insulin sensitivity and secretion in very-low-birth-weight children. *J Clin Endocrinol Metab.* 2004;89:1267-72.

24. Li C, Johnson MS, and Goran MI. Effects of low birth weight on insulin resistance syndrome in caucasian and African-American children. *Diabetes Care.* 2001;24:2035-42.
25. Phillips DI, Goulden P, Syddall HE, et al. Fetal and infant growth and glucose tolerance in the hertfordshire cohort study: a study of men and women born between 1931 and 1939. *Diabetes.* 2005;54 Suppl 2:S145-50.
26. Boney CM, Verma A, Tucker R, et al. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics.* 2005;115:e290-6.
27. Parsons TJ, Power C, and Manor O. Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study. *Bmj.* 2001;323:1331-5.
28. Ehrenberg HM, Mercer BM, and Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. *Am J Obstet Gynecol.* 2004;191:964-8.
29. Ramsay JE, Ferrell WR, Crawford L, et al. Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. *J Clin Endocrinol Metab.* 2002;87:4231-7.
30. Reilly JJ, Armstrong J, Dorosty AR, et al. Early life risk factors for obesity in childhood: cohort study. *Bmj.* 2005;330:1357.
31. Huxley RR. Early nutritional determinants of coronary artery disease: a question of timing? *Am J Clin Nutr.* 2006;84:271-2.
32. Roseboom TJ, van der Meulen JH, Ravelli AC, et al. Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. *Mol Cell Endocrinol.* 2001;185:93-8.
33. Kannisto V, Christensen K, and Vaupel JW. No increased mortality in later life for cohorts born during famine. *Am J Epidemiol.* 1997;145:987-94.
34. Huxley RR and Neil HA. Does maternal nutrition in pregnancy and birth weight influence levels of CHD risk factors in adult life? *Br J Nutr.* 2004;91:459-68.

35. Stanner SA, Bulmer K, Andres C, et al. Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study. *BMJ.* 1997;315:1342-8.
36. Castro LC and Avina RL. Maternal obesity and pregnancy outcomes. *Curr Opin Obstet Gynecol.* 2002;14:601-6.
37. Galtier-Dereure F, Boegner C, and Bringer J. Obesity and pregnancy: complications and cost. *Am J Clin Nutr.* 2000;71:1242S-8S.
38. Marsal K. Intrauterine growth restriction. *Curr Opin Obstet Gynecol.* 2002;14:127-35.
39. Lu GC, Rouse DJ, DuBard M, et al. The effect of the increasing prevalence of maternal obesity on perinatal morbidity. *Am J Obstet Gynecol.* 2001;185:845-9.
40. Surkan PJ, Hsieh CC, Johansson AL, et al. Reasons for increasing trends in large for gestational age births. *Obstet Gynecol.* 2004;104:720-6.
41. Ananth CV and Wen SW. Trends in fetal growth among singleton gestations in the United States and Canada, 1985 through 1998. *Semin Perinatol.* 2002;26:260-7.
42. Napoli C, D'Armiento FP, Mancini FP, et al. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. *J Clin Invest.* 1997;100:2680-90.
43. Napoli C, Glass CK, Witztum JL, et al. Influence of maternal hypercholesterolaemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study. *Lancet.* 1999;354:1234-41.
44. Pettitt DJ, Aleck KA, Baird HR, et al. Congenital susceptibility to NIDDM. Role of intrauterine environment. *Diabetes.* 1988;37:622-8.
45. McMillen IC, Muhlhausler BS, Duffield JA, et al. Prenatal programming of postnatal obesity: fetal nutrition and the regulation of leptin synthesis and secretion before birth. *Proc Nutr Soc.* 2004;63:405-12.

46. Muhlhausler BS, Adam CL, Findlay PA, et al. Increased maternal nutrition alters development of the appetite-regulating network in the brain. *Faseb J.* 2006;20:1257-9.
47. Muhlhausler BS. Programming of the appetite-regulating neural network: a link between maternal overnutrition and the programming of obesity? *J Neuroendocrinol.* 2007;19:67-72.
48. Muhlhausler BS, Roberts CT, McFarlane JR, et al. Fetal leptin is a signal of fat mass independent of maternal nutrition in ewes fed at or above maintenance energy requirements. *Biol Reprod.* 2002;67:493-9.
49. Muhlhausler BS, Duffield JA, and McMillen IC. Increased maternal nutrition stimulates peroxisome proliferator activated receptor-gamma, adiponectin, and leptin messenger ribonucleic acid expression in adipose tissue before birth. *Endocrinology.* 2007;148:878-85.
50. Muhlhausler BS, Roberts CT, Yuen BS, et al. Determinants of fetal leptin synthesis, fat mass, and circulating leptin concentrations in well-nourished ewes in late pregnancy. *Endocrinology.* 2003;144:4947-54.
51. Armitage JA, Taylor PD, and Poston L. Experimental models of developmental programming: consequences of exposure to an energy rich diet during development. *J Physiol.* 2005;565:3-8.
52. Ghosh P, Bitsanis D, Ghebremeskel K, et al. Abnormal aortic fatty acid composition and small artery function in offspring of rats fed a high fat diet in pregnancy. *J Physiol.* 2001;533:815-22.
53. Taylor PD, McConnell J, Khan IY, et al. Impaired glucose homeostasis and mitochondrial abnormalities in offspring of rats fed a fat-rich diet in pregnancy. *Am J Physiol Regul Integr Comp Physiol.* 2005;288:R134-9.
54. Van Assche FA, Holemans K, and Aerts L. Long-term consequences for offspring of diabetes during pregnancy. *Br Med Bull.* 2001;60:173-82.
55. Davidowa H, Li Y, and Plagemann A. Altered neuronal responses to feeding-relevant peptides as sign of developmental plasticity in the hypothalamic regulatory system of body weight. *Zh Vyssh Nerv Deiat Im I P Pavlova.* 2003;53:663-70.

56. Plagemann A, Harder T, Janert U, et al. Malformations of hypothalamic nuclei in hyperinsulinemic offspring of rats with gestational diabetes. *Dev Neurosci.* 1999;21:58-67.
57. Khan IY, Taylor PD, Dekou V, et al. Gender-linked hypertension in offspring of lard-fed pregnant rats. *Hypertension.* 2003;41:168-75.
58. O'Callaghan MJ, Williams GM, Andersen MJ, et al. Prediction of obesity in children at 5 years: a cohort study. *J Paediatr Child Health.* 1997;33:311-6.
59. Sewell MF, Huston-Presley L, Super DM, et al. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. *Am J Obstet Gynecol.* 2006;195.
60. Dempster P and Aitkens S. A new air displacement method for the determination of human body composition. *Med Sci Sports Exerc.* 1995;27:1692-7.
61. Heymsfield SB, Lohman TG, Wang Z, et al., *Human Body Composition*. 2005, Champaign, IL: Human Kinetics.
62. Schmelzle HR and Fusch C. Body fat in neonates and young infants: validation of skinfold thickness versus dual-energy X-ray absorptiometry. *Am J Clin Nutr.* 2002;76:1096-100.
63. Olhager E and Forsum E. Assessment of total body fat using the skinfold technique in full-term and preterm infants. *Acta Paediatr.* 2006;95:21-8.
64. de Bruin NC, van Velthoven KA, Stijnen T, et al. Quantitative assessment of infant body fat by anthropometry and total-body electrical conductivity. *Am J Clin Nutr.* 1995;61:279-86.
65. Koo WW, Walters JC, and Hockman EM. Body composition in neonates: relationship between measured and derived anthropometry with dual-energy X-ray absorptiometry measurements. *Pediatr Res.* 2004;56:694-700.
66. Koo WW, Walters JC, and Hockman EM. Body composition in human infants at birth and postnatally. *J Nutr.* 2000;130:2188-94.
67. Olhager E, Flinke E, Hannerstad U, et al. Studies on human body composition during the first 4 months of life using magnetic resonance imaging and isotope dilution. *Pediatr Res.* 2003;54:906-12.

68. Butte N, Heinz C, Hopkinson J, et al. Fat mass in infants and toddlers: comparability of total body water, total body potassium, total body electrical conductivity, and dual-energy X-ray absorptiometry. *J Pediatr Gastroenterol Nutr.* 1999;29:184-9.
69. de Bruin NC, Westerterp KR, Degenhart HJ, et al. Measurement of fat-free mass in infants. *Pediatr Res.* 1995;38:411-7.
70. Butte NF, Hopkinson JM, Wong WW, et al. Body composition during the first 2 years of life: an updated reference. *Pediatr Res.* 2000;47:578-85.
71. Fiorotto ML, de Bruin NC, Brans YW, et al. Total body electrical conductivity measurements: an evaluation of current instrumentation for infants. *Pediatr Res.* 1995;37:94-100.
72. de Bruin NC, van Velthoven KA, Stijnen T, et al. Body fat and fat-free mass in infants: new and classic anthropometric indexes and prediction equations compared with total-body electrical conductivity. *Am J Clin Nutr.* 1995;61:1195-205.
73. Rigo J, Nyamugabo K, Picaud JC, et al. Reference values of body composition obtained by dual energy X-ray absorptiometry in preterm and term neonates. *J Pediatr Gastroenterol Nutr.* 1998;27:184-90.
74. Hammami M, Koo WW, and Hockman EM. Body composition of neonates from fan beam dual energy X-ray absorptiometry measurement. *JPEN J Parenter Enteral Nutr.* 2003;27:423-6.
75. Urlando A, Dempster P, and Aitkens S. A new air displacement plethysmograph for the measurement of body composition in infants. *Pediatr Res.* 2003;53:486-92.
76. Sainz RD and Urlando A. Evaluation of a new pediatric air-displacement plethysmograph for body-composition assessment by means of chemical analysis of bovine tissue phantoms. *Am J Clin Nutr.* 2003;77:364-70.
77. Ma G, Yao M, Liu Y, et al. Validation of a new pediatric air-displacement plethysmograph for assessing body composition in infants. *Am J Clin Nutr.* 2004;79:653-60.

78. Yao M, Nommsen-Rivers L, Dewey K, et al. Preliminary evaluation of a new pediatric air displacement plethysmograph for body composition assessment in infants. *Acta Diabetol.* 2003;40 Suppl 1:S55-8.
79. Koo WW. Body composition measurements during infancy. *Ann N Y Acad Sci.* 2000;904:383-92.
80. Davies PS and Lucas A. The prediction of total body fatness in early infancy. *Early Hum Dev.* 1990;21:193-8.
81. Davies PS and Lucas A. Quetelet's index as a measure of body fatness in young infants. *Early Hum Dev.* 1989;20:135-41.
82. Weststrate JA and Deurenberg P. Body composition in children: proposal for a method for calculating body fat percentage from total body density or skinfold-thickness measurements. *Am J Clin Nutr.* 1989;50:1104-15.
83. Dauncey MJ, Gandy G, and Gairdner D. Assessment of total body fat in infancy from skinfold thickness measurements. *Arch Dis Child.* 1977;52:223-7.
84. Berne RM and Levy MN, *Physiology*. 4th ed. 1998, St. Louis: Mosby.
85. Di Cianni G, Miccoli R, Volpe L, et al. Intermediate metabolism in normal pregnancy and in gestational diabetes. *Diabetes Metab Res Rev.* 2003;19:259-70.
86. Catalano PM, Tyzbir ED, Roman NM, et al. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am J Obstet Gynecol.* 1991;165:1667-72.
87. Catalano PM, Huston L, Amini SB, et al. Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. *Am J Obstet Gynecol.* 1999;180:903-16.
88. Goldstein BJ and Muller-Wieland D, *Textbook of Type 2 Diabetes*. 2003, United Kingdom: Martin Dunitz.
89. Metzger BE and Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. *Diabetes Care.* 1998;21 Suppl 2:B161-7.
90. Catalano PM and Ehrenberg HM. The short- and long-term implications of maternal obesity on the mother and her offspring. *Bjog.* 2006;113:1126-33.

91. *Institute of Medicine (US). Nutritional status and weight gain. In: Nutrition During Pregnancy*. 1990, National Academcy Press: Washington, DC. p. 27-233.
92. Ehrenberg HM, Huston-Presley L, and Catalano PM. The influence of obesity and gestational diabetes mellitus on accretion and the distribution of adipose tissue in pregnancy. *Am J Obstet Gynecol.* 2003;189:944-8.
93. King JC. Maternal obesity, metabolism, and pregnancy outcomes. *Annu Rev Nutr.* 2006;26:271-91.
94. Ravelli GP, Stein ZA, and Susser MW. Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med.* 1976;295:349-53.
95. Painter RC, De Rooij SR, Bossuyt PM, et al. Early onset of coronary artery disease after prenatal exposure to the Dutch famine. *Am J Clin Nutr.* 2006;84:322-7.
96. Moulton CR. Age and chemical development in mammals. *J Biol Chem.* 1923;57:79-97.
97. Barker DJ, Winter PD, Osmond C, et al. Weight in infancy and death from ischaemic heart disease. *Lancet.* 1989;2:577-80.
98. Hales CN, Barker DJ, Clark PM, et al. Fetal and infant growth and impaired glucose tolerance at age 64. *Bmj.* 1991;303:1019-22.
99. Leon DA, Lithell HO, Vagero D, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915-29. *Bmj.* 1998;317:241-5.
100. Jarvelin MR, Sovio U, King V, et al. Early life factors and blood pressure at age 31 years in the 1966 northern Finland birth cohort. *Hypertension.* 2004;44:838-46.
101. Uiterwaal CS, Anthony S, Launer LJ, et al. Birth weight, growth, and blood pressure: an annual follow-up study of children aged 5 through 21 years. *Hypertension.* 1997;30:267-71.
102. Rich-Edwards JW, Stampfer MJ, Manson JE, et al. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *Bmj.* 1997;315:396-400.

103. Barker DJ, Martyn CN, Osmond C, et al. Growth in utero and serum cholesterol concentrations in adult life. *Bmj.* 1993;307:1524-7.
104. Kajantie E. Fetal origins of stress-related adult disease. *Ann N Y Acad Sci.* 2006;1083:11-27.
105. van Assche FA and Aerts L. The fetal endocrine pancreas. *Contrib Gynecol Obstet.* 1979;5:44-57.
106. Mackenzie HS and Brenner BM. Fewer nephrons at birth: a missing link in the etiology of essential hypertension? *Am J Kidney Dis.* 1995;26:91-8.
107. Martyn CN and Greenwald SE. A hypothesis about a mechanism for the programming of blood pressure and vascular disease in early life. *Clin Exp Pharmacol Physiol.* 2001;28:948-51.
108. Konje JC, Bell SC, Morton JJ, et al. Human fetal kidney morphometry during gestation and the relationship between weight, kidney morphometry and plasma active renin concentration at birth. *Clin Sci (Lond).* 1996;91:169-75.
109. Martin H, Hu J, Gennser G, et al. Impaired endothelial function and increased carotid stiffness in 9-year-old children with low birthweight. *Circulation.* 2000;102:2739-44.
110. Martin H, Gazelius B, and Norman M. Impaired acetylcholine-induced vascular relaxation in low birth weight infants: implications for adult hypertension? *Pediatr Res.* 2000;47:457-62.
111. Phillips DI and Barker DJ. Association between low birthweight and high resting pulse in adult life: is the sympathetic nervous system involved in programming the insulin resistance syndrome? *Diabet Med.* 1997;14:673-7.
112. Galland BC, Taylor BJ, Bolton DP, et al. Heart rate variability and cardiac reflexes in small for gestational age infants. *J Appl Physiol.* 2006;100:933-9.
113. Wilson SJ, Ross JJ, and Harris AJ. A critical period for formation of secondary myotubes defined by prenatal undernourishment in rats. *Development.* 1988;102:815-21.
114. Dwyer CM and Stickland NC. Does the anatomical location of a muscle affect the influence of undernutrition on muscle fibre number? *J Anat.* 1992;181 (Pt 2):373-6.

115. Ogata ES, Swanson SL, Collins JW, Jr., et al. Intrauterine growth retardation: altered hepatic energy and redox states in the fetal rat. *Pediatr Res.* 1990;27:56-63.

116. Lane RH, Flozak AS, Ogata ES, et al. Altered hepatic gene expression of enzymes involved in energy metabolism in the growth-retarded fetal rat. *Pediatr Res.* 1996;39:390-4.

117. Lane RH, Kelley DE, Gruetzmacher EM, et al. Uteroplacental insufficiency alters hepatic fatty acid-metabolizing enzymes in juvenile and adult rats. *Am J Physiol Regul Integr Comp Physiol.* 2001;280:R183-90.

118. Young JB. Developmental origins of obesity: a sympathoadrenal perspective. *Int J Obes (Lond).* 2006;30 Suppl 4:S41-9.

119. Matthews SG. Early programming of the hypothalamo-pituitary-adrenal axis. *Trends Endocrinol Metab.* 2002;13:373-80.

120. Matthews SG. Antenatal glucocorticoids and programming of the developing CNS. *Pediatr Res.* 2000;47:291-300.

121. Phillips DI, Barker DJ, Fall CH, et al. Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome? *J Clin Endocrinol Metab.* 1998;83:757-60.

122. Phillips DI, Walker BR, Reynolds RM, et al. Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. *Hypertension.* 2000;35:1301-6.

123. Ahima RS. Adipose tissue as an endocrine organ. *Obesity (Silver Spring).* 2006;14 Suppl 5:242S-249S.

124. Kieffer TJ and Habener JF. The adipoinsular axis: effects of leptin on pancreatic beta-cells. *Am J Physiol Endocrinol Metab.* 2000;278:E1-E14.

125. Matsuda J, Yokota I, Iida M, et al. Serum leptin concentration in cord blood: relationship to birth weight and gender. *J Clin Endocrinol Metab.* 1997;82:1642-4.

126. Phillips DI, Fall CH, Cooper C, et al. Size at birth and plasma leptin concentrations in adult life. *Int J Obes Relat Metab Disord.* 1999;23:1025-9.

127. Kabali C and Werler MM. Pre-pregnant body mass index, weight gain and the risk of delivering large babies among non-diabetic mothers. *Int J Gynaecol Obstet.* 2007.
128. Wu G, Bazer FW, Cudd TA, et al. Maternal nutrition and fetal development. *J Nutr.* 2004;134:2169-72.
129. Rogers I. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. *Int J Obes Relat Metab Disord.* 2003;27:755-77.
130. Tuvemo T, Cnattingius S, and Jonsson B. Prediction of male adult stature using anthropometric data at birth: a nationwide population-based study. *Pediatr Res.* 1999;46:491-5.
131. Karlberg J and Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. *Pediatr Res.* 1995;38:733-9.
132. Seidman DS, Laor A, Gale R, et al. A longitudinal study of birth weight and being overweight in late adolescence. *Am J Dis Child.* 1991;145:782-5.
133. Fall CH, Osmond C, Barker DJ, et al. Fetal and infant growth and cardiovascular risk factors in women. *Bmj.* 1995;310:428-32.
134. Ros HS, Lichtenstein P, Ekbom A, et al. Tall or short? Twenty years after preeclampsia exposure in utero: comparisons of final height, body mass index, waist-to-hip ratio, and age at menarche among women, exposed and unexposed to preeclampsia during fetal life. *Pediatr Res.* 2001;49:763-9.
135. Kahn HS, Narayan KM, Williamson DF, et al. Relation of birth weight to lean and fat thigh tissue in young men. *Int J Obes Relat Metab Disord.* 2000;24:667-72.
136. Phillips DI and Young JB. Birth weight, climate at birth and the risk of obesity in adult life. *Int J Obes Relat Metab Disord.* 2000;24:281-7.
137. Sorensen HT, Sabroe S, Rothman KJ, et al. Relation between weight and length at birth and body mass index in young adulthood: cohort study. *Bmj.* 1997;315:1137.

138. Lithell HO, McKeigue PM, Berglund L, et al. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50-60 years. *Bmj.* 1996;312:406-10.
139. Eide MG, Oyen N, Skjaerven R, et al. Size at birth and gestational age as predictors of adult height and weight. *Epidemiology.* 2005;16:175-81.
140. Binkin NJ, Yip R, Fleshood L, et al. Birth weight and childhood growth. *Pediatrics.* 1988;82:828-34.
141. Fisch RO, Bilek MK, and Ulstrom R. Obesity and leanness at birth and their relationship to body habitus in later childhood. *Pediatrics.* 1975;56:521-8.
142. Kromeyer-Hauschild K, Zellner K, Jaeger U, et al. Prevalence of overweight and obesity among school children in Jena (Germany). *Int J Obes Relat Metab Disord.* 1999;23:1143-50.
143. Schroeder DG and Martorell R. Fatness and body mass index from birth to young adulthood in a rural Guatemalan population. *Am J Clin Nutr.* 1999;70:137S-144S.
144. He Q, Ding ZY, Fong DY, et al. Risk factors of obesity in preschool children in China: a population-based case--control study. *Int J Obes Relat Metab Disord.* 2000;24:1528-36.
145. Bavdekar A, Yajnik CS, Fall CH, et al. Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? *Diabetes.* 1999;48:2422-9.
146. Zive MM, McKay H, Frank-Spohrer GC, et al. Infant-feeding practices and adiposity in 4-y-old Anglo- and Mexican-Americans. *Am J Clin Nutr.* 1992;55:1104-8.
147. Whitaker RC, Pepe MS, Wright JA, et al. Early adiposity rebound and the risk of adult obesity. *Pediatrics.* 1998;101:E5.
148. Valdez R, Athens MA, Thompson GH, et al. Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia.* 1994;37:624-31.
149. Phillips DI. Relation of fetal growth to adult muscle mass and glucose tolerance. *Diabet Med.* 1995;12:686-90.

150. Yarbrough DE, Barrett-Connor E, Kritz-Silverstein D, et al. Birth weight, adult weight, and girth as predictors of the metabolic syndrome in postmenopausal women: the Rancho Bernardo Study. *Diabetes Care.* 1998;21:1652-8.
151. Vestbo E, Damsgaard EM, Froland A, et al. Birth weight and cardiovascular risk factors in an epidemiological study. *Diabetologia.* 1996;39:1598-602.
152. Malina RM, Katzmarzyk PT, and Beunen G. Birth weight and its relationship to size attained and relative fat distribution at 7 to 12 years of age. *Obes Res.* 1996;4:385-90.
153. Esposito-Del Puente A, Scalfi L, De Filippo E, et al. Familial and environmental influences on body composition and body fat distribution in childhood in southern Italy. *Int J Obes Relat Metab Disord.* 1994;18:596-601.
154. Sobal J and Stunkard AJ. Socioeconomic status and obesity: a review of the literature. *Psychol Bull.* 1989;105:260-75.
155. Maffeis C. Aetiology of overweight and obesity in children and adolescents. *Eur J Pediatr.* 2000;159 Suppl 1:S35-44.
156. Burke V, Beilin LJ, and Dunbar D. Family lifestyle and parental body mass index as predictors of body mass index in Australian children: a longitudinal study. *Int J Obes Relat Metab Disord.* 2001;25:147-57.
157. Whitaker RC, Wright JA, Pepe MS, et al. Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med.* 1997;337:869-73.
158. Guillaume M, Lapidus L, Beckers F, et al. Familial trends of obesity through three generations: the Belgian-Luxembourg child study. *Int J Obes Relat Metab Disord.* 1995;19 Suppl 3:S5-9.
159. Li C, Kaur H, Choi WS, et al. Additive interactions of maternal prepregnancy BMI and breast-feeding on childhood overweight. *Obes Res.* 2005;13:362-71.
160. Abrams BF and Laros RK, Jr. Prepregnancy weight, weight gain, and birth weight. *Am J Obstet Gynecol.* 1986;154:503-9.
161. Haiek L and Lederman SA. The relationship between maternal weight for height and term birth weight in teens and adult women. *J Adolesc Health Care.* 1989;10:16-22.

162. Frisancho AR. Prenatal compared with parental origins of adolescent fatness. *Am J Clin Nutr.* 2000;72:1186-90.

163. Stettler N, Tershakovec AM, Zemel BS, et al. Early risk factors for increased adiposity: a cohort study of African American subjects followed from birth to young adulthood. *Am J Clin Nutr.* 2000;72:378-83.

164. Duran-Tauleria E, Rona RJ, and Chinn S. Factors associated with weight for height and skinfold thickness in British children. *J Epidemiol Community Health.* 1995;49:466-73.

165. Maffeis C, Micciolo R, Must A, et al. Parental and perinatal factors associated with childhood obesity in north-east Italy. *Int J Obes Relat Metab Disord.* 1994;18:301-5.

166. Gallaher MM, Hauck FR, Yang-Oshida M, et al. Obesity among Mescalero preschool children. Association with maternal obesity and birth weight. *Am J Dis Child.* 1991;145:1262-5.

167. Catalano PM, Thomas A, Huston-Presley L, et al. Increased fetal adiposity: a very sensitive marker of abnormal in utero development. *Am J Obstet Gynecol.* 2003;189:1698-704.

168. Rossner S and Ohlin A. Maternal body weight and relation to birth weight. *Acta Obstet Gynecol Scand.* 1990;69:475-8.

169. Fomon SJ, Haschke F, Ziegler EE, et al. Body composition of reference children from birth to age 10 years. *Am J Clin Nutr.* 1982;35:1169-75.

170. Tepper RS, Merth IT, Newth CJ, et al., *Measurement of functional residual capacity in infants by helium dilution and nitrogen washout*, in *Infant Respiratory Function Testing*. 1996, Wiley-Liss: New York. p. 165-189.

171. Stocks J, Marchard F, Kraemer R, et al., *Plethysmographis assessment of functional residual capacity and airway reisistance*, in *Infant Respiratory Function Testing*. 1996, Wiley-Liss: New York.

172. Stick S, *Measurements during tidal breathing*, in *Infant Respiratory Function Testing*. 1996, Wiley-Liss: New York. p. 117-138.

173. Cohen J, *Statistical power analysis for the behavioral sciences* 2nd ed. 1988, Hillsdale, NJ: Lawrence Earlbaum Associates.

174. Nagy G. Management of gestational diabetes. *Zentralbl Gynakol.* 1993;115:147-53.
175. Ehrenberg HM, Dierker L, Milluzzi C, et al. Prevalence of maternal obesity in an urban center. *Am J Obstet Gynecol.* 2002;187:1189-93.
176. Szostak-Wegierek D, Szamotulska K, and Szponar L. [Influence of maternal nutrition on infant birthweight]. *Ginekol Pol.* 2004;75:692-8.
177. Kirchengast S and Hartmann B. Maternal prepregnancy weight status and pregnancy weight gain as major determinants for newborn weight and size. *Ann Hum Biol.* 1998;25:17-28.
178. Shapiro C, Sutija VG, and Bush J. Effect of maternal weight gain on infant birth weight. *J Perinat Med.* 2000;28:428-31.
179. Barker DJ. The intrauterine environment and adult cardiovascular disease. *Ciba Found Symp.* 1991;156:3-10; discussion 10-6.
180. Barker DJ and Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet.* 1986;1:1077-81.
181. Barker M, Robinson S, Osmond C, et al. Birth weight and body fat distribution in adolescent girls. *Arch Dis Child.* 1997;77:381-3.
182. Barker DJ, Eriksson JG, Forsen T, et al. Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol.* 2002;31:1235-9.
183. Barker DJ. The fetal origins of adult hypertension. *J Hypertens Suppl.* 1992;10:S39-44.
184. Barker DJ, Hales CN, Fall CH, et al. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia.* 1993;36:62-7.
185. Barker DJ, Osmond C, and Law CM. The intrauterine and early postnatal origins of cardiovascular disease and chronic bronchitis. *J Epidemiol Community Health.* 1989;43:237-40.
186. Byrne CD and Phillips DI. Fetal origins of adult disease: epidemiology and mechanisms. *J Clin Pathol.* 2000;53:822-8.
187. Barker DJ. The developmental origins of insulin resistance. *Horm Res.* 2005;64 Suppl 3:2-7.

188. Kanadys WM. [Pre-pregnancy body mass, gestational weight gain and birth weight]. *Ginekol Pol.* 1998;69:1223-7.

189. Shao D. [The relationship between maternal body weight index and fetal weight and delivery mode]. *Zhonghua Fu Chan Ke Za Zhi.* 1995;30:718-20.

190. Sun B, Li J, and Song Q. [Influence of prepregnancy weight and maternal weight gain on pregnancy outcome]. *Zhonghua Fu Chan Ke Za Zhi.* 1998;33:71-3.

191. Kramer MS and Joseph KS. Enigma of fetal/infant-origins hypothesis. *Lancet.* 1996;348:1254-5.

192. Andreasyan K, Ponsonby AL, Dwyer T, et al. Higher maternal dietary protein intake in late pregnancy is associated with a lower infant ponderal index at birth. *Eur J Clin Nutr.* 2007;61:498-508.

193. Catalano PM. Management of obesity in pregnancy. *Obstet Gynecol.* 2007;109:419-33.

194. Weiss JL, Malone FD, Emig D, et al. Obesity, obstetric complications and cesarean delivery rate--a population-based screening study. *Am J Obstet Gynecol.* 2004;190:1091-7.

195. Catalano PM, Tyzbir ED, Allen SR, et al. Evaluation of fetal growth by estimation of neonatal body composition. *Obstet Gynecol.* 1992;79:46-50.

196. Plagemann A, Harder T, Kohlhoff R, et al. Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes. *Int J Obes Relat Metab Disord.* 1997;21:451-6.

APPENDIX A

(IRB Approval Letter)

The University of Oklahoma
Health Sciences Center
INSTITUTIONAL REVIEW BOARD

IRB Number: 12828
Approval Date: May 05, 2006

May 09, 2006

David Fields, Ph.D.
Univ of OK, Dept of Health & Sport Sciences
940 N. E. 13th, CHO 2B2426
Oklahoma City, OK 73104-5066

RE: Prenatal Maternal Weight Status and It's Impact on Fetal Birth Weight and Composition

Dear Dr. Fields:

On behalf of the Institutional Review Board (IRB), I have reviewed and granted expedited approval of the above-referenced research study. This study meets the criteria for expedited approval category #4. It is my judgment as Chairperson of the IRB that the rights and welfare of individuals who may be asked to participate in this study will be respected; that the proposed research, including the process of obtaining informed consent, will be conducted in a manner consistent with the requirements of 45 CFR 46 or 21 CFR 50 & 56 as amended; and that the research involves no more than minimal risk to participants.

This letter documents approval to conduct the research as described:

Advertisement Dated: July 26, 2005 Newspaper ad
IRB Application Dated: July 26, 2005
Consent form - Parental Dated: February 18, 2005
Protocol Dated: February 16, 2005
Priv - Research Auth 1 Dated: January 06, 2005

As principal investigator of this protocol, it is your responsibility to make sure that this study is conducted as approved. Any modifications to the protocol or consent form, initiated by you or by the sponsor, will require prior approval, which you may request by completing a protocol modification form. All study records, including copies of signed consent forms, must be retained for three (3) years after termination of the study.

It is a condition of this approval that you report promptly to the IRB any serious, unanticipated adverse events experienced by subjects in the course of this research, whether or not they are directly related to the study protocol. These adverse events include, but may not be limited to, any experience that is fatal or immediately life-threatening, is permanently disabling, requires (or prolongs) inpatient hospitalization, or is a congenital anomaly, cancer or overdose. For multi-site protocols, the IRB must be informed of serious adverse events at all sites.

The approval granted expires on April 30, 2007. Should you wish to maintain this protocol in an active status beyond that date, you will need to provide the IRB with an IRB Application for Continuing Review (Progress Report) summarizing study results to date. The IRB will request an IRB Application for Continuing Review from you approximately three months before the anniversary date of your current approval.

If you have questions about these procedures, or need any additional assistance from the IRB, please call the IRB office at (405) 271-2045 or send an email to irb@ouhsc.edu. Finally, please review your professional liability insurance to make sure your coverage includes the activities in this study.

Sincerely yours,

Karen J. Beckman, M.D.
Chair, Institutional Review Board

Ltr_Prot_Fappv_Exp

Post Office Box 26901 • 1000 S.L. Young Blvd., Room 176
Oklahoma City, Oklahoma 73190 • (405) 271-2045 • FAX: (405) 271-1677

APPENDIX B

(Informed Consent and HIPAA)

CONSENT FORM

UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

Study Title: "Prenatal Maternal Weight Status and Its Impact on Fetal Birth Weight and Composition"

Principal Investigator: David A. Fields, PhD.

This is a research study. Research studies involve only individuals who choose to participate. Please take your time to make your decision, and do not make your decision until you feel you have all the information you need about the project. Participating in this study, the use of the term "You" refers to "You and Your Child" and addresses both the participant and the parent or legally authorized representative.

Why Have I Been Asked To Participate In This Study?
You are being asked to take part in this study because you gave birth to a baby within the last 45 days.

Why Is This Study Being Done?
This study is being done to help determine what, if any, impact your weight and diabetic status before becoming pregnant has on your baby's weight and body composition.

How Many People Will Take Part In The Study?
A total of 180 mother-baby pairs will take part in the study.

What Is Involved In The Study?
Health Status: We will obtain some preliminary information regarding your health from your physician and medical record chart. This will include recording your age, height, pre-pregnancy weight, and race. We will not be obtaining your current weight. A medical history will be taken on your baby and your baby's weight, length, and head circumference will also be measured.

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Picture of the Pea Pod.

Body Composition Testing: The amount of fat your baby has will be measured in an instrument called a Pea Pod. Your baby will be placed naked inside the Pea Pod for approximately 3 minutes. Your baby will lie in an enclosed chamber, but there is a viewing window where you can see your baby (and your baby can see you) for the entire test. It is a clean, warm, comfortable environment for your baby. At no time will you ever be away from your baby or be unable to see your baby. The Pea Pod is totally painless for your baby and similar to being placed on his/her back in a small bassinette.

Food Recall: You will be asked the foods and drinks they ate over the last four days and for the immediate past twenty-four hours. Your food recall will be sent to the University of Alabama in Birmingham for analysis (your recall will be unidentified).

Optional Testing

Blood Draw: During your third trimester of pregnancy 10 cc of blood will be drawn from the mother. This will be done to measure glucose levels and markers of inflammation, both of which could play a role in your infants body weight and composition. Your blood will be sent to the University of Alabama in Birmingham for analysis (your blood will be unidentified). This blood draw is optional. You still can participate in the study without giving blood.

_____ Yes, I agree to have blood drawn.
_____ No, I do not agree to have blood drawn

How Long Will It Take?

We anticipate it will take approximately 20 to 30 minutes to obtain the information on you and your baby and to perform the Pea Pod testing on your baby. You will not have to do anything else for the study or come back at a later date.

Where Will I Have To Go?

You and your baby will go to The Children's Hospital at OU Medical Center on the Health Sciences Center Campus.

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What Are The Risks of The Study?

Risks / Discomforts: There are very minimal risks and discomforts involved during your participation in this research study. All research procedures will be conducted by qualified researchers and medical personnel. The potential risk and discomforts associated with the research study are listed below:

Body Composition Test: Your infant may cry upon being placed in the Pea Pod due to physical separation from you.

What Are The Benefits to Taking Part in The Study?
There are no benefits in participating in this study. The information you contribute will assist with determining the possible influence of mother's body status before becoming pregnant on the body composition of her infant. We hope that these studies will help us determine the factors that contribute to a child being underweight, normal weight, or overweight.

What Other Options Are There?
Instead of being in this study, you have the option to not participate.

What About Confidentiality?

Efforts will be made to keep your personal information confidential. You will not be identifiable by name or description in any reports or publications about this study. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. You will be asked to sign a separate authorization form for use or sharing of your protected health information. There are organizations that may inspect and/or copy your research record for quality assurance and data analysis. These organizations include the OUHSC Institutional Review Board.

What Are the Costs?
Transportation will be your only cost. Parking is free.

Will I be paid for the Study?
You will be reimbursed with a $50 Simon Visa Gift Card for participating in the study.

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What Are My Rights As A Participant?
Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. If you agree to take part and then decide against it, you can withdraw for any reason. Leaving the study will not result in any penalty or loss of benefits that you would otherwise receive. You understand that you have the right to access the medical information that has been collected about you as a part of this research study. However, you agree that you may not have access to this medical information until the entire research study has completely finished and you consent to this temporary restriction. We will tell you about any new information that may affect your health, welfare or willingness to stay in this study.

Whom Do I call If I have Questions or Problems?
If you have questions about the study or have a research–related injury, contact David A. Fields, Ph.D. at (405) 271-8001 extension 43083, (405) 271-6764, or at (405) 325-7358. For questions regarding your rights as a research subject, contact the OUHSC Director, Human Research Participant Protection Program at (405) 271-2045.

Signature:
By signing this form, you are agreeing to participate in this research study under the conditions described. You have not given up any of your legal rights or released any individual or institution from liability for negligence. You have been given an opportunity to ask questions. You will be given a copy of this consent document. Your signature indicates that you have decided to participate, that you have read (or been read) the information provided above, and that you have received a copy of this consent form.

Infant Printed Name	Date	
Mother Signature	Parent (Mother) Printed Name	Date
Father Signature	Parent (Mother) Printed Name	Date
Person Obtaining Consent	Date	

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IRB No.: 12828

AUTHORIZATION TO USE or DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH

An additional Informed Consent Document for Research Participation may also be required.Form 2 must be used for research involving psychotherapy notes.

Title of Research Project: **Prenatal Maternal Weight Status and its Impact on Fetal Birth Weight and Composition**

Leader of Research Team: **David A. Fields, Ph.D**

Address: **OUCP Diabetes & Endocrinology, 940 NE 13th, CH 2B2426, OKC, OK 73104**

Phone Number**: (405) 271-6764 ext: 43083 or (405) 325-7358**

If you decide to join this research project, University of Oklahoma Health Sciences Center (OUHSC) researchers may use or share (disclose) information about you that is considered to be protected health information for their research. Protected health information will be called private information in this Authorization.

Private Information To Be Used or Shared. Federal law requires that researchers get your permission (authorization) to use or share your private information. If you give permission, the researchers may use or share *your and* your baby's private information with the people identified in this authorization any private information related to this research from your medical records and from any test results. Information, used or shared, may include all information relating to any tests, procedures, surveys, or interviews as outlined in the consent form, medical records and charts, name, address, telephone number, date of birth, race, and government-issued identification number.

Purposes for Using or Sharing Private Information. If you give permission, the researchers may use your private information to better understand how maternal weight prior to pregnancy impacts the birth weight and composition of their offspring.

Other Use and Sharing of Private Information. If you give permission, the researchers may also use your private information to develop new procedures or commercial products. They may share your private information with the research sponsor, the OUHSC Institutional Review Board, auditors and inspectors who check the research, and government agencies such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS). The researchers may also share your private information with Drs. Kenneth C. Copeland and Casey Hester and their research team at the University of Oklahoma Health Science Center. Additionally, the unidintified blood and food recalls will be sent to the University of Alabama in Birmingham.

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Confidentiality. Although the researchers may report their findings in scientific journals or meetings, they will not identify you in their reports. The researchers will try to keep your information confidential, but confidentiality is not guaranteed. Any person or organization receiving the information based on this authorization could re-release the information to others and federal law would no longer protect it.

YOU MUST UNDERSTAND THAT YOUR PROTECTED HEALTH INFORMATION MAY INCLUDE INFORMATION REGARDING ANY CONDITIONS CONSIDERED AS A COMMUNICABLE OR VENEREAL DISEASE WHICH MAY INCLUDE, BUT ARE NOT LIMITED TO, DISEASES SUCH AS HEPATITIS, SYPHILIS, GONORRHEA, AND HUMAN IMMUNODEFICIENCY VIRUS ALSO KNOWN AS ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS).

Voluntary Choice. The choice to give OUHSC researchers permission to use or share your private information for their research is voluntary. It is completely up to you. No one can force you to give permission. However, you must give permission for OUHSC researchers to use or share your private health information if you want to participate in the research and if you revoke your authorization, you can no longer participate in this study.

Refusing to give permission will not affect your ability to get routine treatment or health care from OUHSC.

Revoking Permission. If you give the OUHSC researchers permission to use or share your private information, you have a right to revoke your permission whenever you want. However, revoking your permission will not apply to information that the researchers have already used, relied on, or shared.

End of Permission. Unless you revoke it, permission for OUHSC researchers to use or share your private information for their research will "never end". You may revoke your permission at any time by writing to:

Privacy Official
University of Oklahoma Health Sciences Center
PO Box 26901, Oklahoma City, OK 73190
If you have questions call: (405) 271-2511

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Giving Permission. By signing this form, you give OUHSC and OUHSC's researchers led by David A. Fields, Ph.D., permission to share your private information for the research project called "Prenatal Maternal Weight Status and its Impact on Fetal Birth Weight and Composition".

Patient/Subject Name: _____

_____ _____
Signature of Patient-Subject Date
or Parent if subject is a child

Or

_____ _____
Signature of Legal Representative** Date

**If signed by a Legal Representative of the Patient-Subject, provide a description of the relationship to the Patient-Subject and the Authority to Act as Legal Representative:

_____

OUHSC may ask you to produce evidence of your relationship.

A signed copy of this form must be given to the Patient-Subject or the Legal Representative at the time this signed form is provided to the researcher or his representative.

IRB No.: 12828

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APPENDIX C

(Data Collection Form)

Participant ID: CA- __ __ __- __ __
Group ID: _____

INITIAL VISIT

ELIGIBILITY

Review potential participant eligibility using the standard screening script and Recruitment database. Use gestation calculator and enter answers below. Answer summary questions.

Baby's Name: _____

Today's date: ____/____/____ (mm/dd/yy)

First day of last menstrual period: ____/____/____ (mm/dd/yy)

Estimated due date: ____/____/____ (mm/dd/yy)

Actual date of birth: ____/____/____ (mm/dd/yy)

Length of gestation: ____/____ weeks / days

Today's age: _____ days

SCREENING

Check one answer for each question:	**YES**	**NO**
Healthy male or female full term infant with gestational age of ≥37 weeks and <42 weeks?		
Infant discharged from the hospital ≤28 days of delivery?		
Mother age at time of delivery between 18-45 years old?		
Did infant stay in the hospital >4 days?		
Did mother smoke during pregnancy/lactation?		
Did mother use alcohol (>1 drink /week) during pregnancy?		
Does infant have a known chromosomal or severe congenital abnormality?		
Do mom / baby meet all inclusion criteria (no shaded answers)?		

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Check one answer for each question:	**YES**	**NO**
Did mom have type 1, type 2 diabetes or gestational diabetes during pregnancy (circle which one)?		
Was diabetes present before pregnancy?		
Did mother have pre-eclampsia?		
Participating in the "Normative" study?		
BABY'S FAMILY HISTORY (Mother, Father and Grandparents)	**YES**	**NO**
Diabetes (list relative and age of onset)		
Heart Disease (list relative and age of onset)		
Hypertension (list relative and age of onset)		
Polycystic ovaries, infertility, hirsutism (list relative and age of onset)		
Thyroid Disease (list relative and age of onset)		
Smoking in immediate family (list relative and age of onset)		

INFORMED CONSENT

☐ In a verbal discussion, the parent(s) was informed of all aspects of the study using the written informed consent and HIPAA documents. The parent(s) was then given time to privately re-read the informed consent and HIPAA documents. The parent(s) was given an opportunity to ask questions. All questions were answered prior to signing both documents. A signed copy of both forms was given to the parent(s).

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DIET ASSESSMENT

How often does baby nurse? _____

How many times per day (24 hours) does baby nurse?_____

Does baby usually nurse on one side or both at each feed?_____

How long does baby nurse each time?_____ Minutes

DEMOGRAPHICS

Mother's Ethnic Background: _____

Father's Ethnic Background: _____

Address:_____

City, State, Zip_____

Phone(s):_____ Type: _____

_____ Type: _____

E-mail Address: _____

Total Family Income: _____ (per year)

Infant:

Sex: ☐ Male ☐ Female

Race:
- ☐ White
- ☐ Black or African American
- ☐ American Indian / Alaska Native
- ☐ Asian
- ☐ Native Hawaiian / Pacific Islander
- ☐ Other: _____
- ☐ Two or more races: _____

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Mother

Self-reported pre-pregnancy weight: _____

Self-reported weight gain during pregnancy: _____

Age at birth: _____

Today	Measure 1
Weight (kg)	
Height (cm)	

Infant

Today	Measure 1
Weight (kg)	
Length (cm)	
Head circumference (cm)	

PeaPod

☐ Obtained, copy of results placed in study file

☐ Not obtained. Reason: _____

Check any that apply:

☐ Calm ☐ Crying

☐ Urine ☐ Bowel Movement

Comments: _____

_____

Check one answer for each question:	YES	NO
4 day food recall completed?		
24 Hour Food Recall Completed?		

Provide compensation for today's visit:

Compensation: _____

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APPENDIX D

(Unadjusted Infant Outcome Variables)

	Normal (N=33)	**Overweight/ Obese (N=39)**
Birth weight (g)	3433.8 ± 333.7	3367.0 ± 446.8
%fat	12.5 ± 5.0	13.7 ± 5.1
Fat mass (g)	412.7 ± 255.5	449.1 ± 284.5
Fat-free mass (g)	3308.5 ± 313.8	3162.8 ± 382.6